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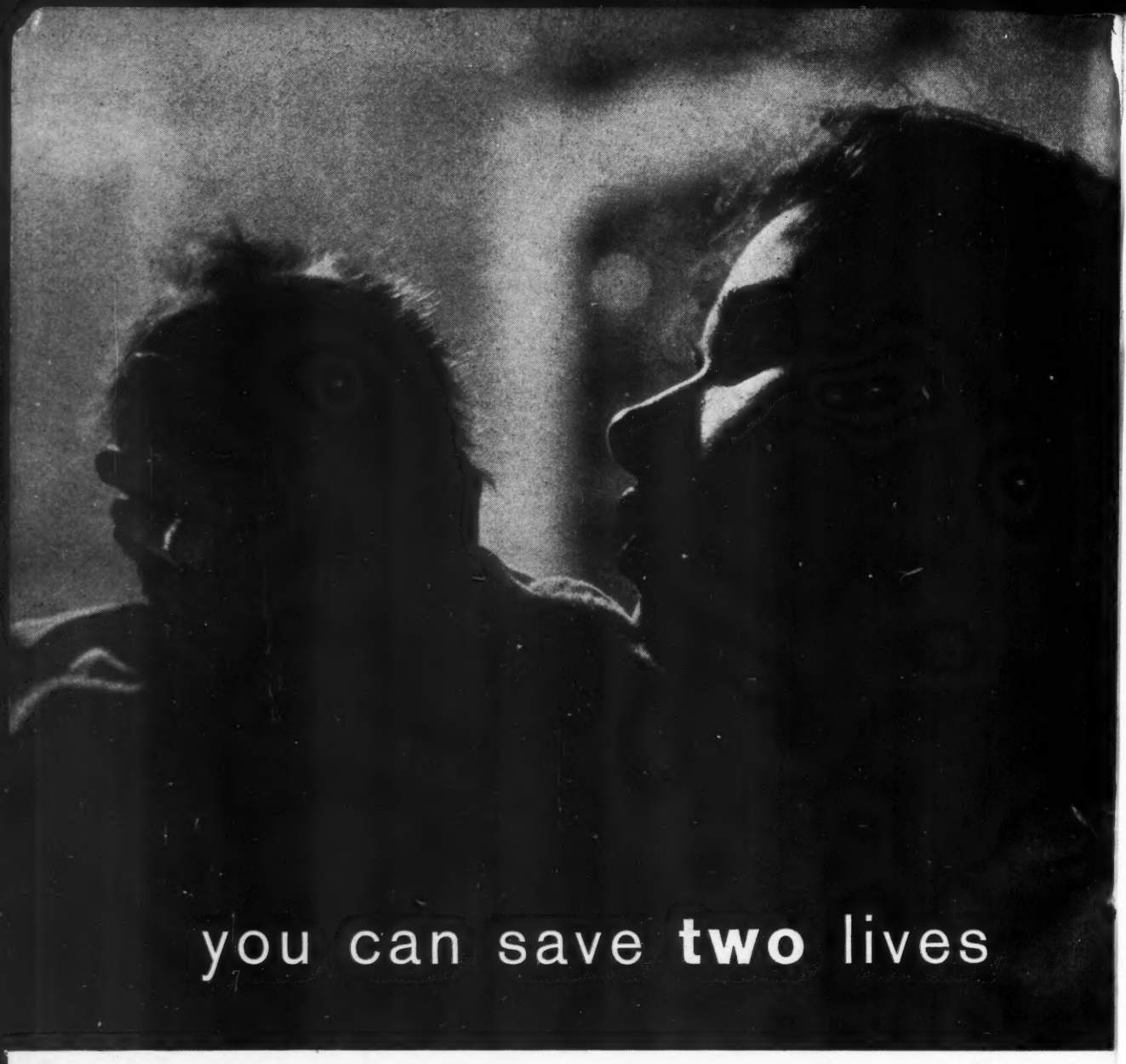

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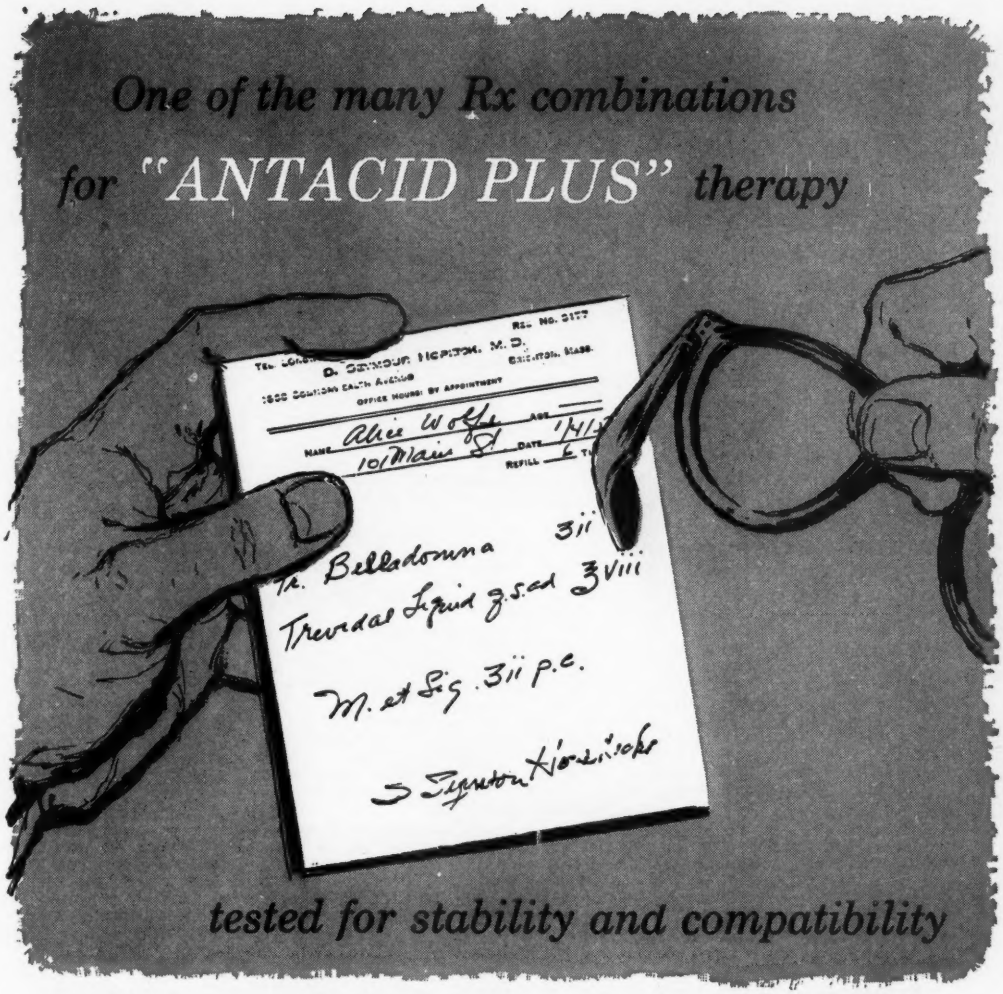

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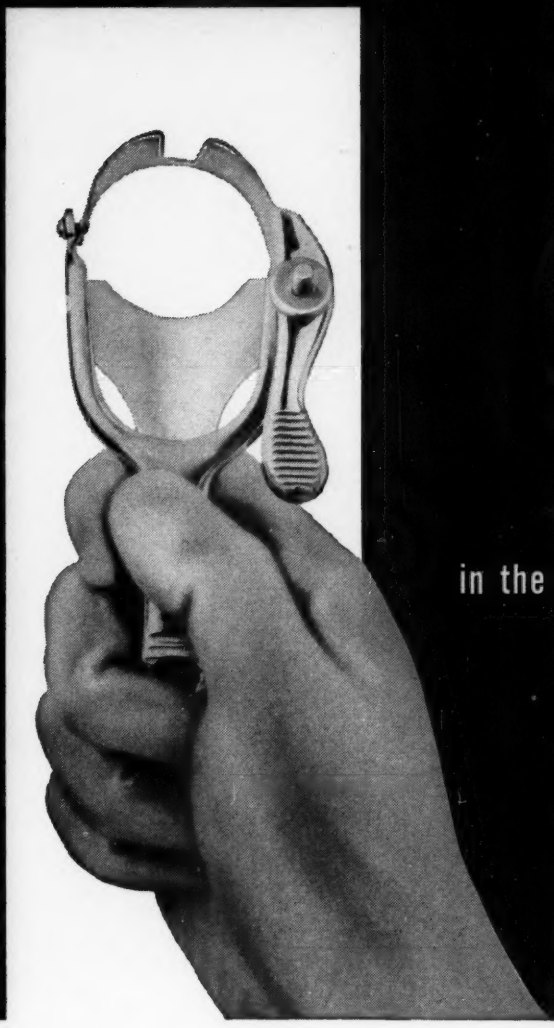

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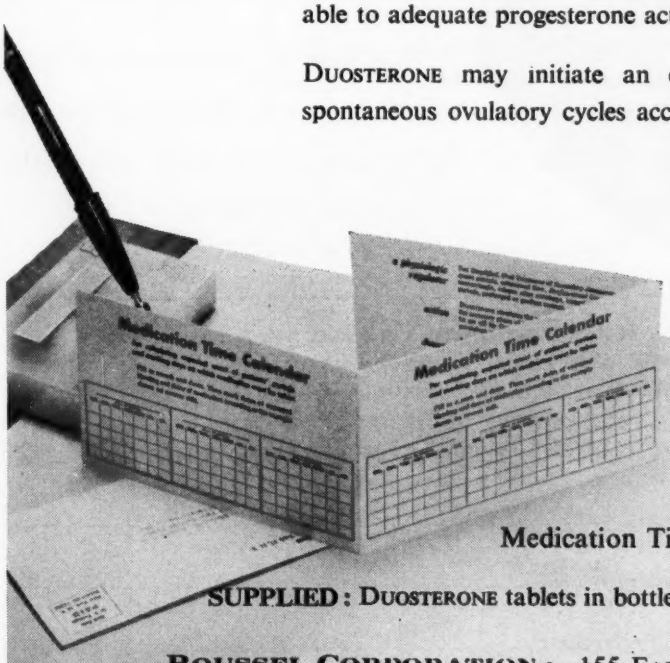

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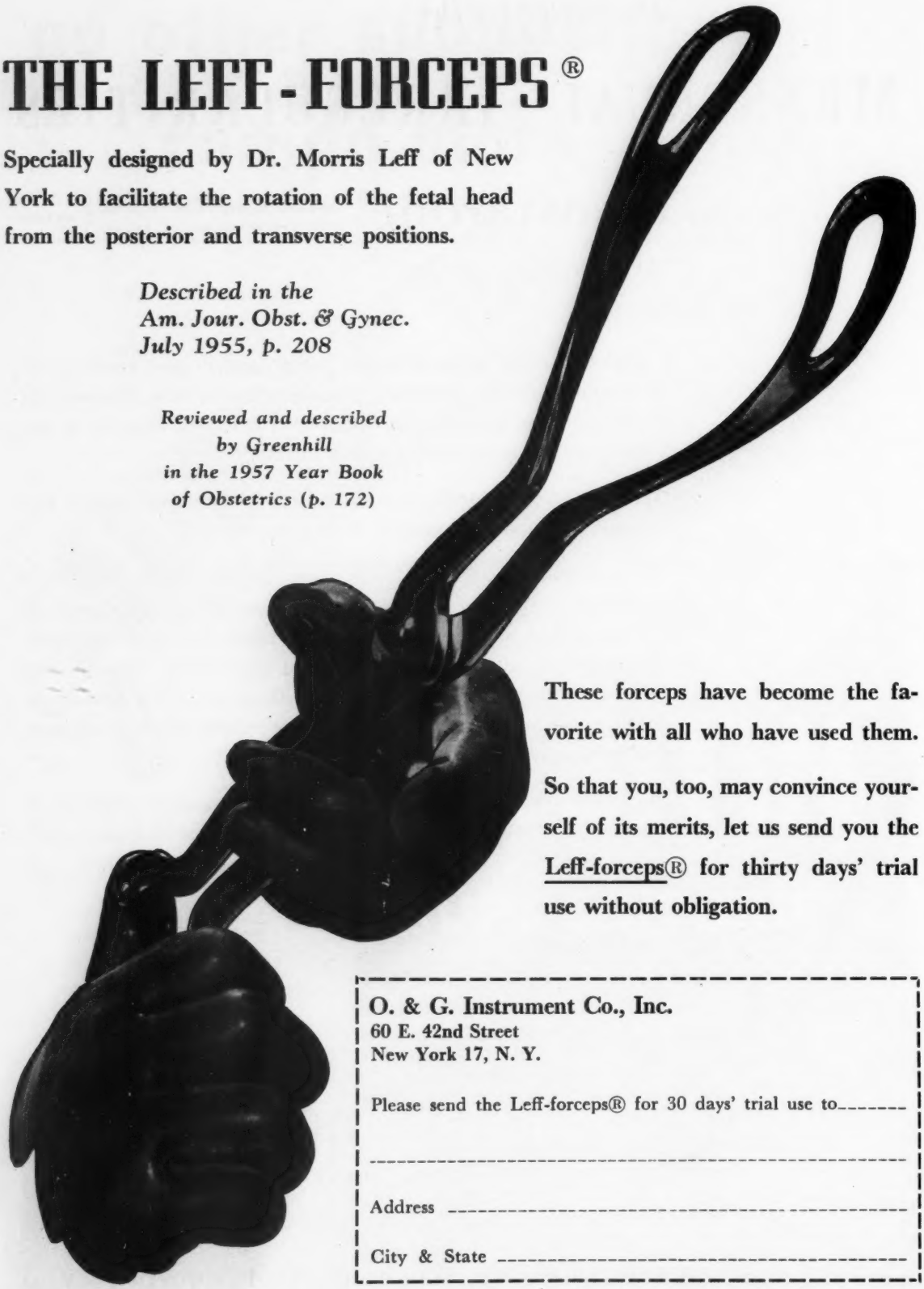

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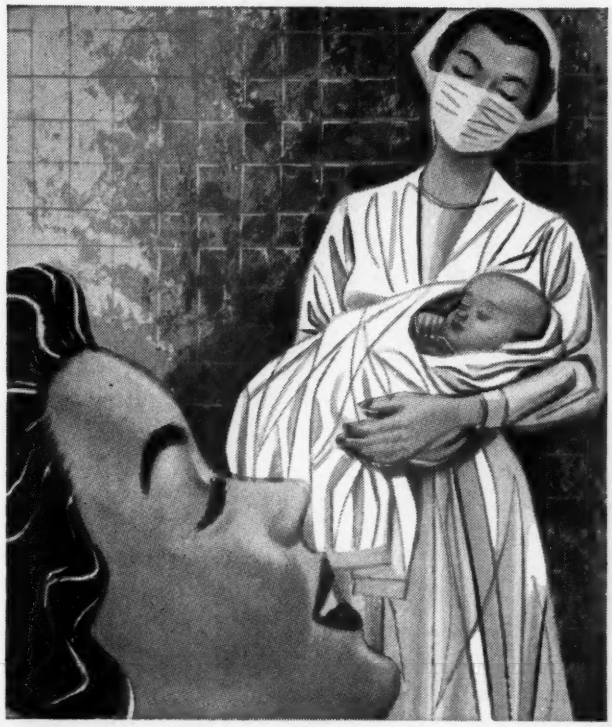

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When narcotics are a standard part of the obstetrical preparation, prophylactic use of NALLINE offers many benefits. Injected five to fifteen minutes before delivery, NALLINE reduces significantly the need for resuscitation and time required for the newborn infant to gasp and cry. In the mother, NALLINE combats narcotic-induced respiratory and circulatory depression and facilitates induction of inhalation anesthesia. NALLINE antagonizes morphine, heroin, methadone, Dromoran®, Levo-Dromoran®, Nisentil®, Dilaudid®, Pantopon®, and Demerol®.

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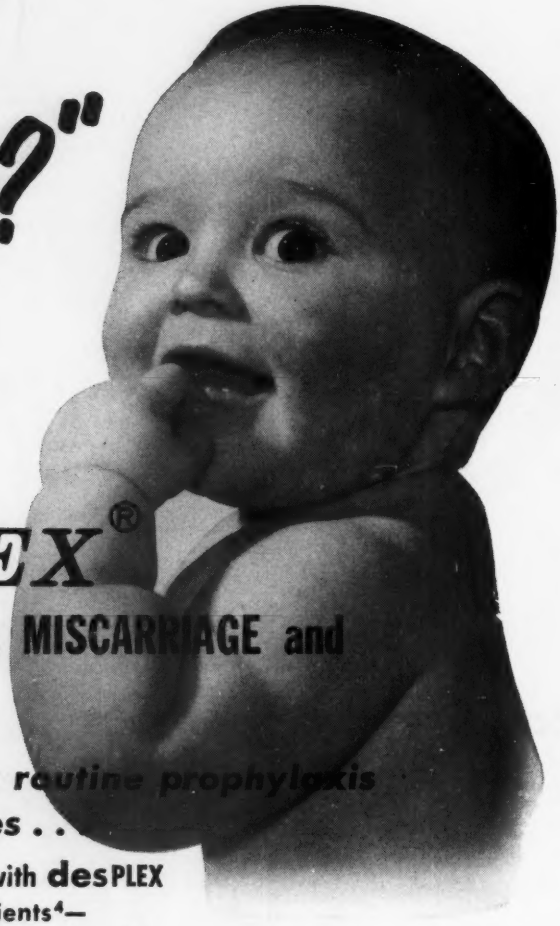

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96 per cent live delivery with desPLEX in one series of 1200 patients[4]— — bigger and stronger babies, too.[cf. 1]

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REFERENCES

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2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
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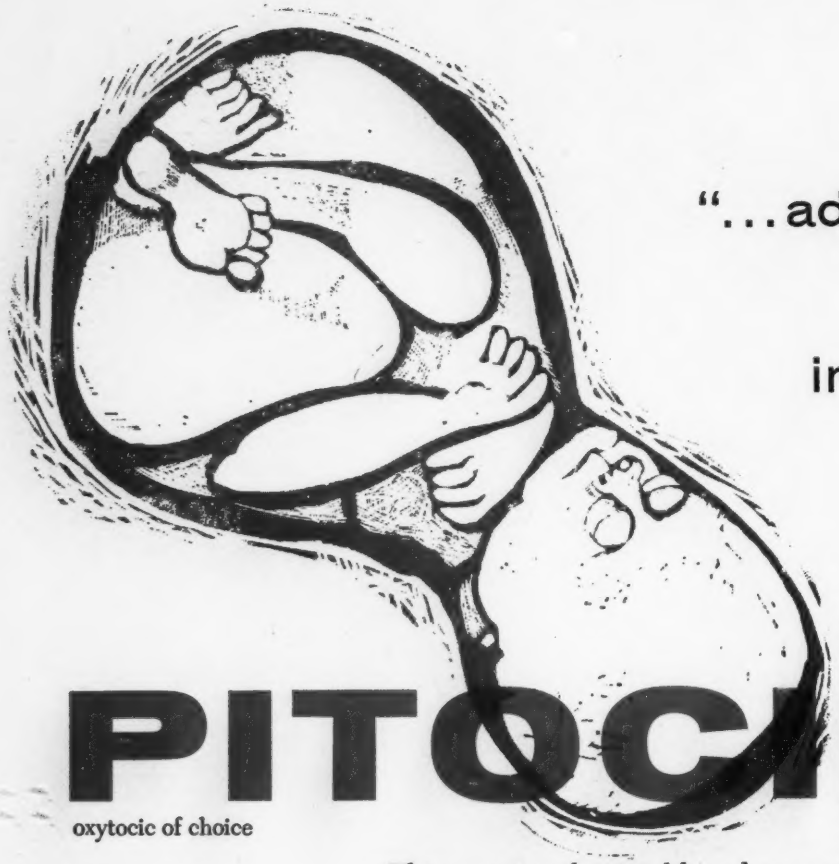

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(1) Williams, P. C., & McMahon, T. B.: *Am. J. Obst. & Gynec.* **71**:1264, 1956.
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systemic antibacterial action, Azo Can
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in one tablet:

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antibacterial—analgesic
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Each AZO GANTRISIN tablet contains 0.5 Gm Gantrisin plus 50 mg of phenylazo-diamino-pyridine HCl.

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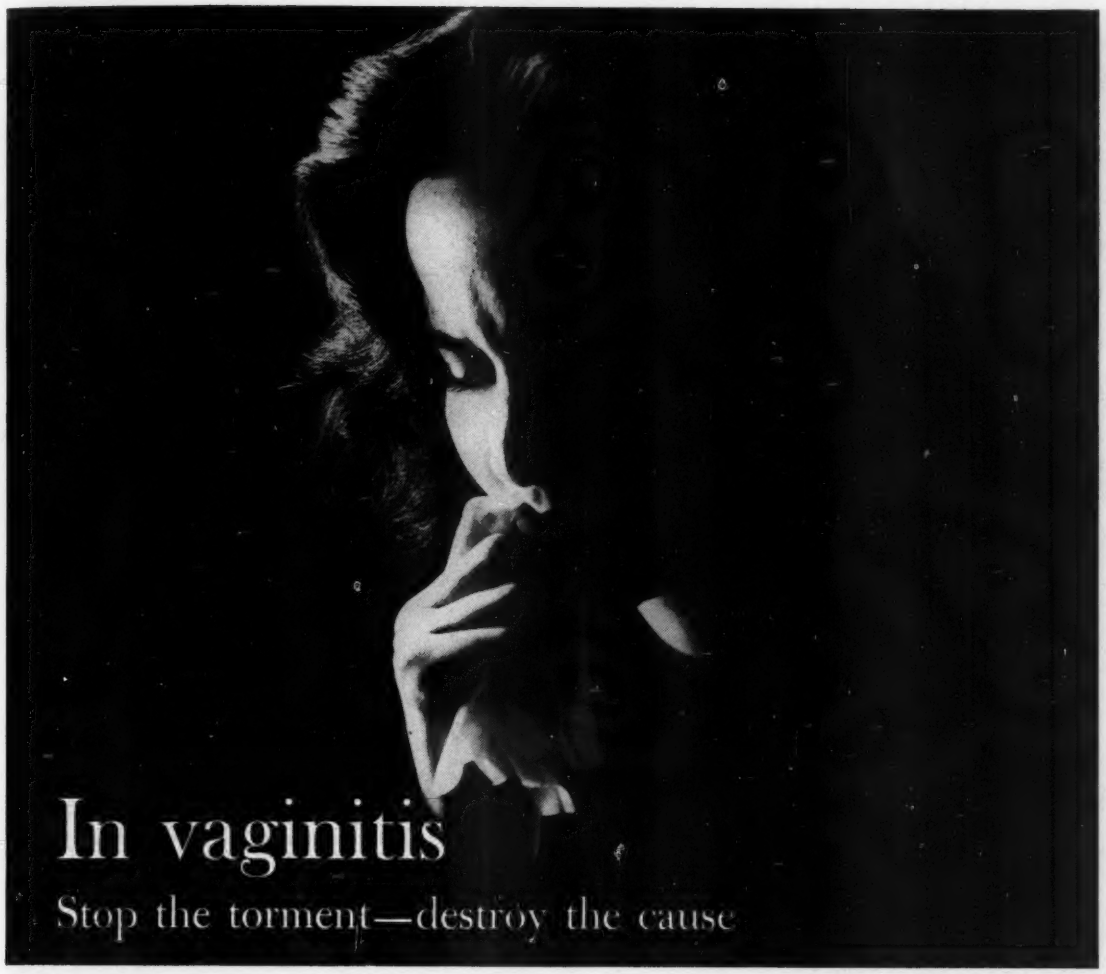

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Improved

in trichomonal vaginitis –
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in monilial vaginitis –
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Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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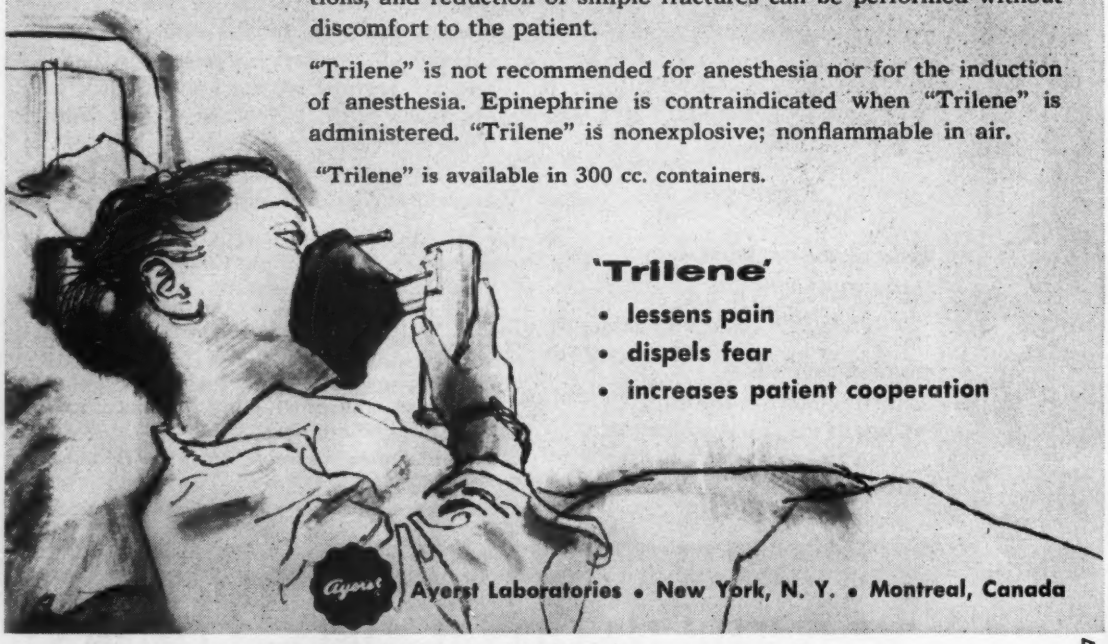

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REFERENCES:

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3. Editorial: J. A. M. A. *159*:116 (Sept. 10) 1955.

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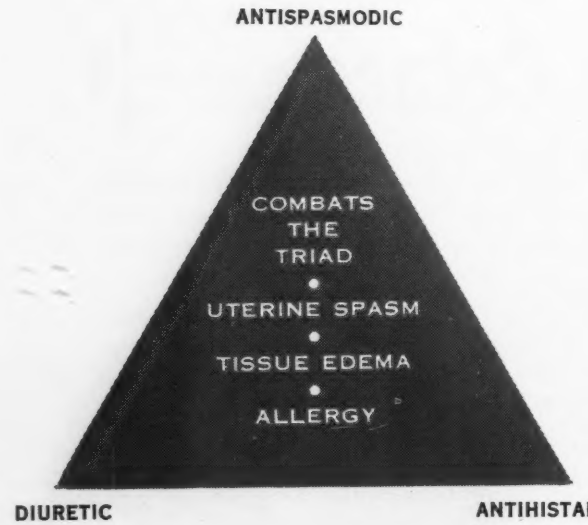

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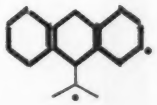

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—*Oxygenation in Obstetrics:* J. C. Dunlap and W. W. Brown; Obstetrics & Gynecology, 3:496, May, 1954.

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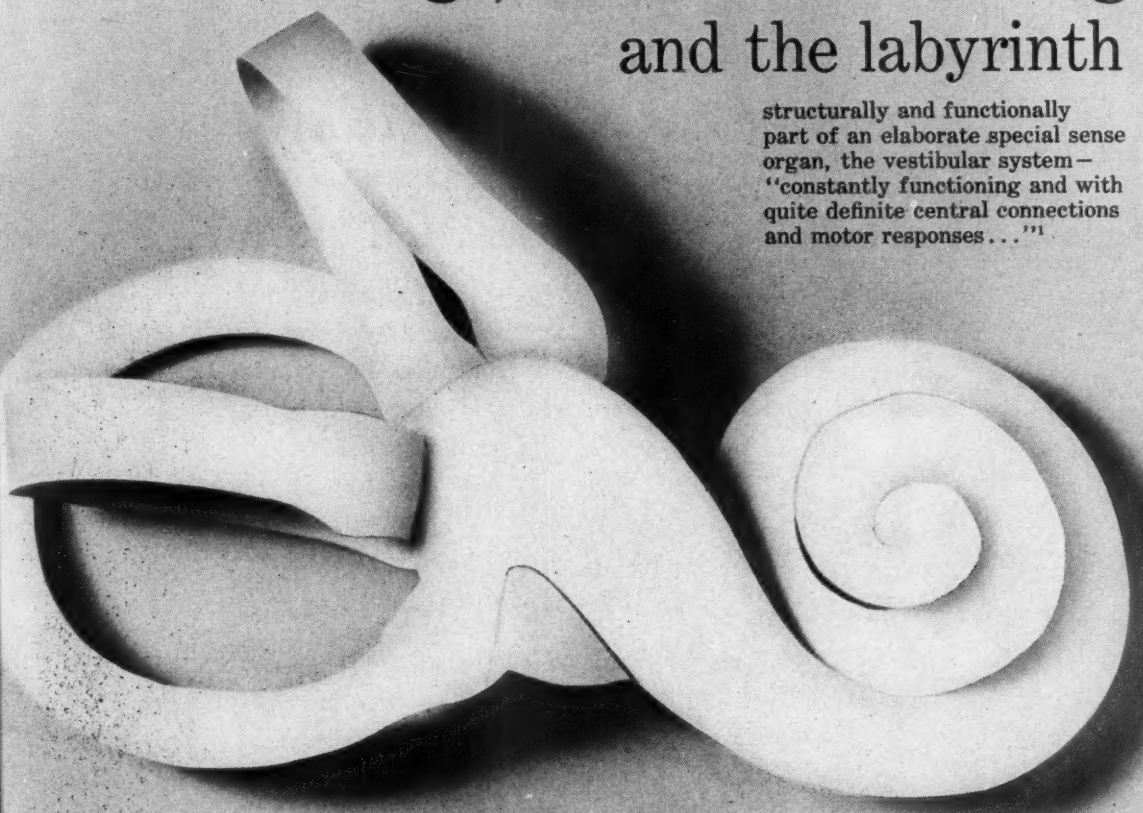
vertigo, nausea and vomiting and the labyrinth



structurally and functionally part of an elaborate special sense organ, the vestibular system—"constantly functioning and with quite definite central connections and motor responses..."[1]

controlled by BONAMINE*

BRAND OF MECLIZINE HYDROCHLORIDE

—effectively blocking responsible physiological pathways to provide immediate and long-lasting relief from vertigo, nausea and vomiting associated with

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Bonamine is available as scored, tasteless tablets, 25 mg.; also in the form of mint-flavored chewing tablets, 25 mg.

References: 1. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, The Blakiston Company, 1947, pp. 111-133. 2. Kinney, J. J.: J. M. Soc. New Jersey *53*:128 (March) 1956. 3. Weil, L. L.: Florida J. Gen. Pract. *4*:9 (July) 1954. 4. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. *160*:755 (March 3) 1956.

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1. Locket, S.: Brit. M.J. *1*:809 (Apr. 2) 1955.

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2. Wright, W.T., Jr., et al.: J. Kansas M. Soc. *57*:410 (July) 1956.

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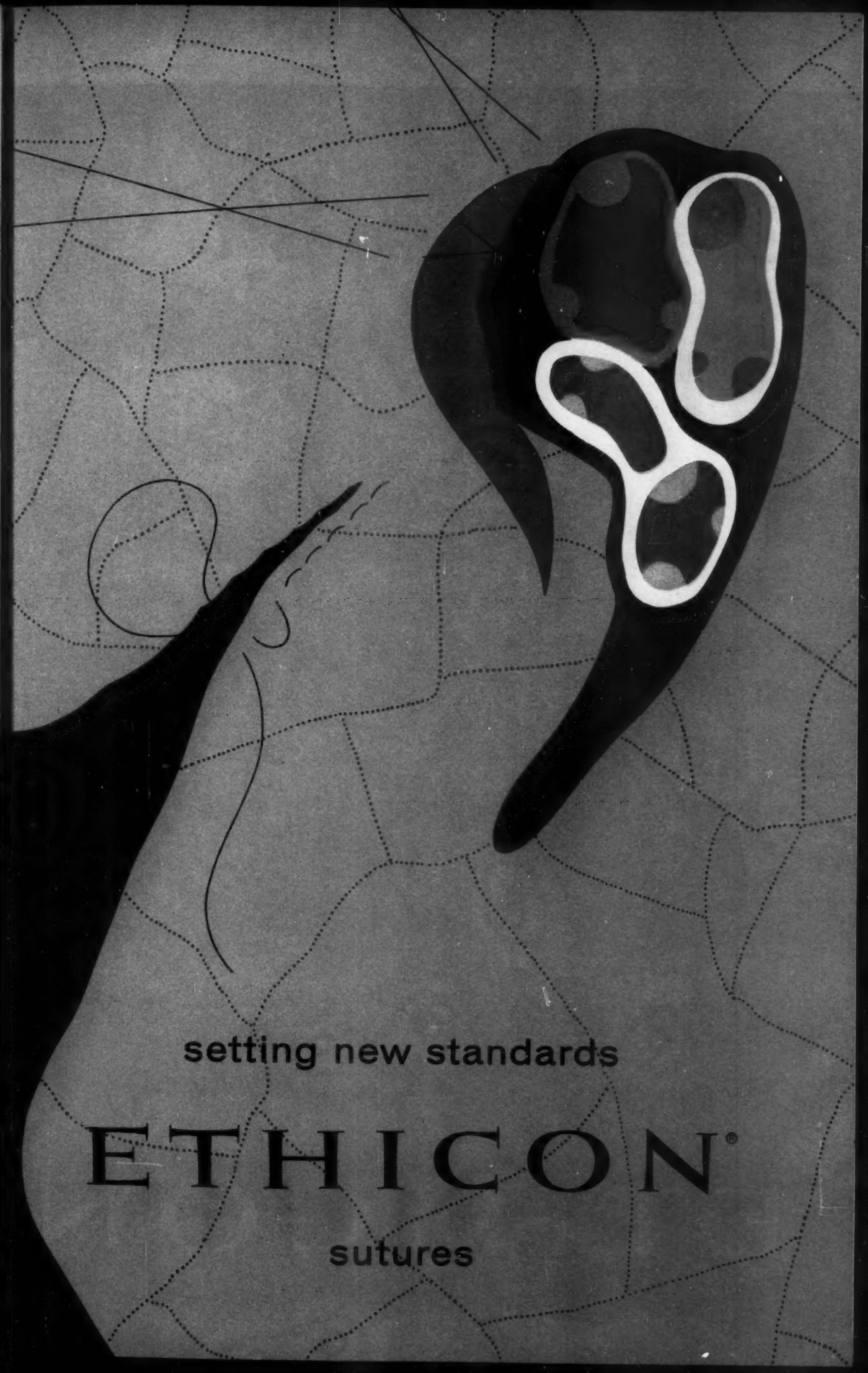
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1. Eichner, E.; Goler, G. G.; Sharzer, S., and Horowitz, B.: Obst. & Gynec. 6:511, 1955.

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2. Greenblatt, R. B., and Brown, N. H.: Am. J. Obst. & Gynec. 63:1361, 1952.

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1. Eichner, E.; Goler, G. G.; Sharzer, S., and Horowitz, B.: Obst. & Gynec. 6:511, 1955.

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3. Bennet, E. T., and McCann, E. C.: J. Maine M. A. 45:225, 1954.

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4. Nulsen, R. O.; Carmon, W. B., and Hendrick, H. O.: Am. J. Obst. & Gynec. 65:1048, 1953.

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1. Dieckmann, W. J., and Priddle, H. D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, Am. J. Obst. & Gynec. 57:541, (March) 1949.
2. Neary, E. R.: Am. J. Med. Sc. 212:76 (July) 1946.
3. Kelly, H. T.: Pennsylvania M. J. 51:999 (June) 1948.

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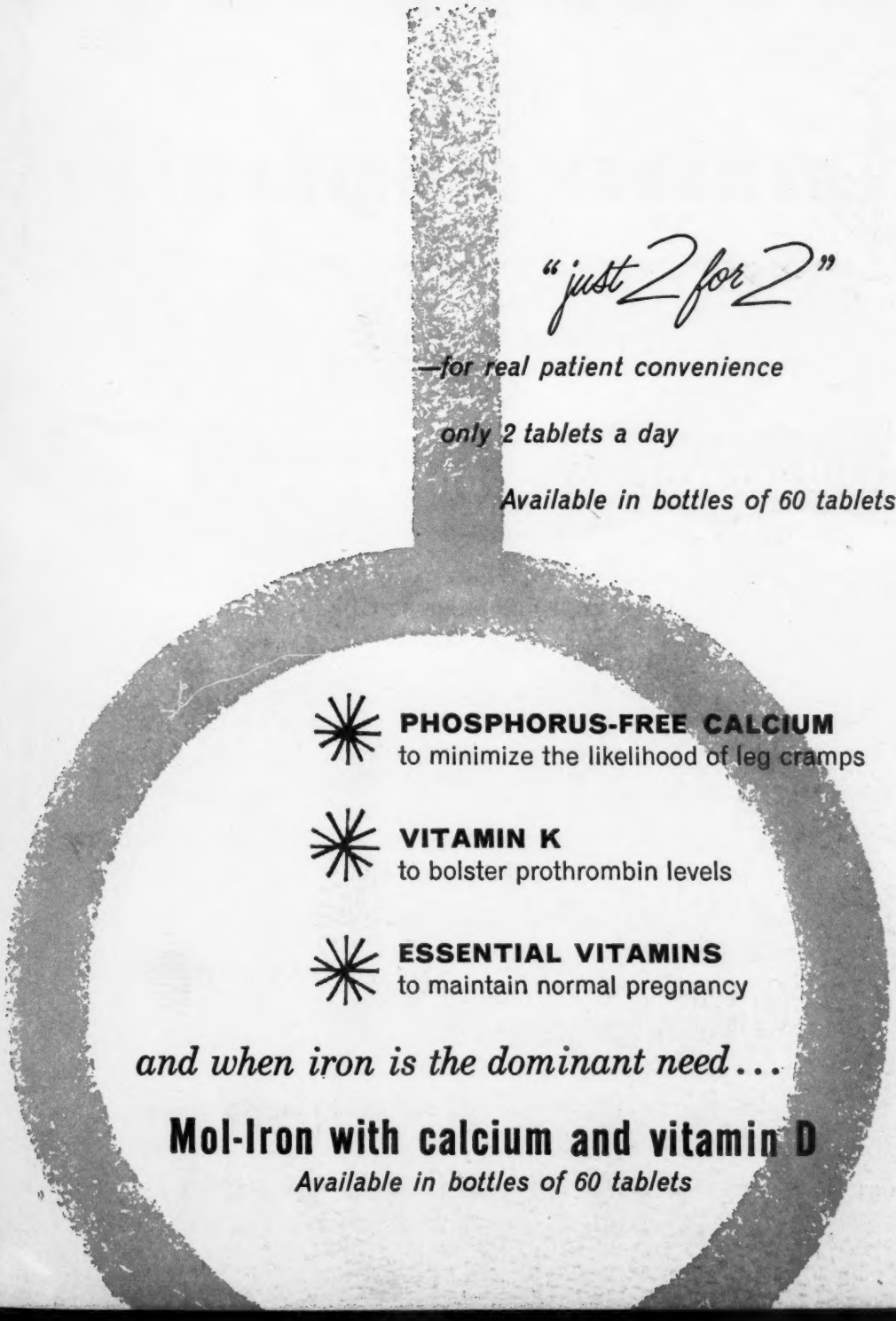

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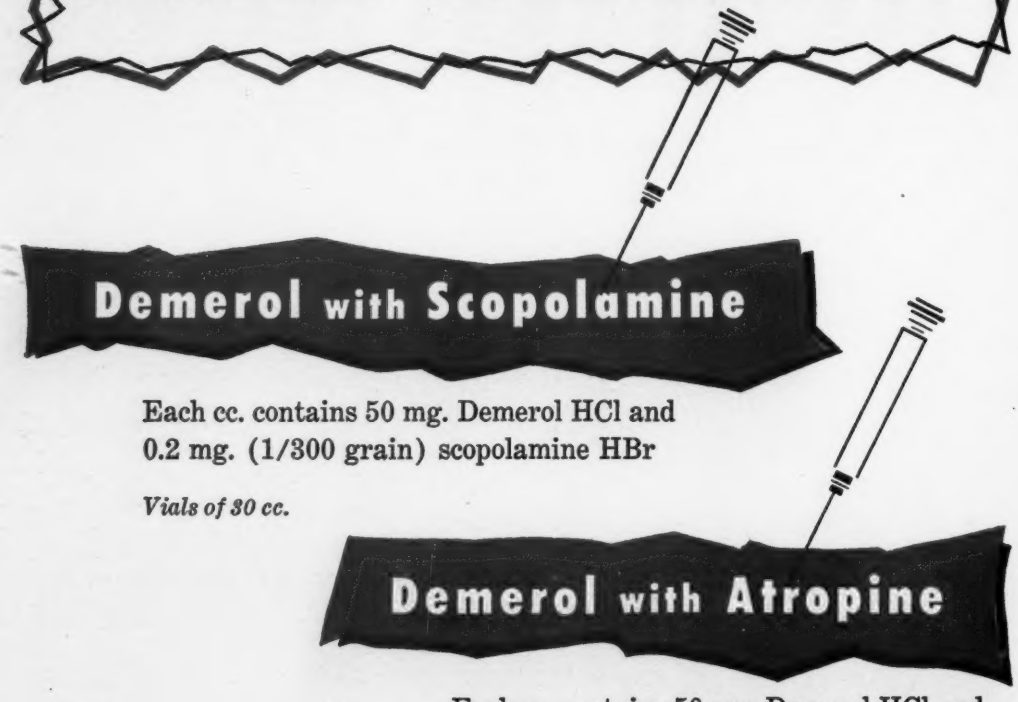

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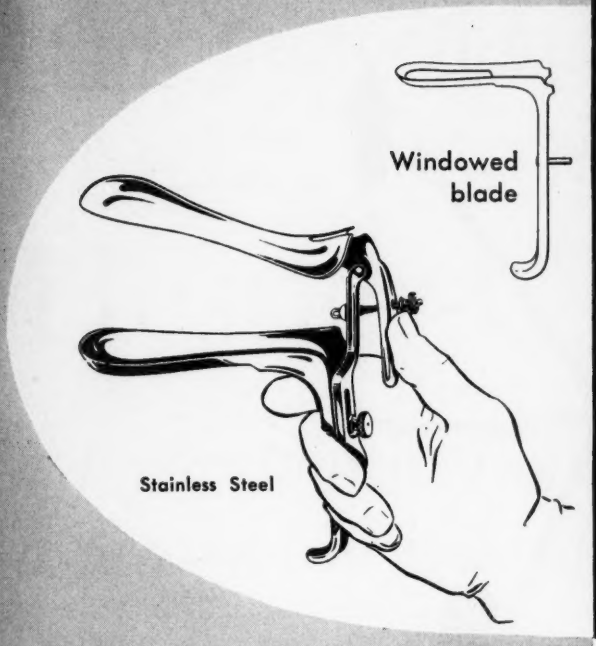

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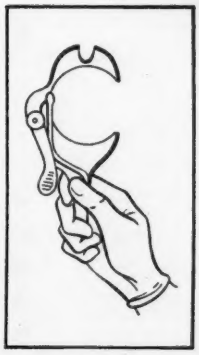

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References: 1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953. 2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954. 3. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955. 4. Javert, C. T.: Obst. & Gynec. *3*:420, 1954. 5. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 6. Barishaw, S. B.: Exp. Med. & Surg. 7:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest. Dis. *17*:92, 1950.

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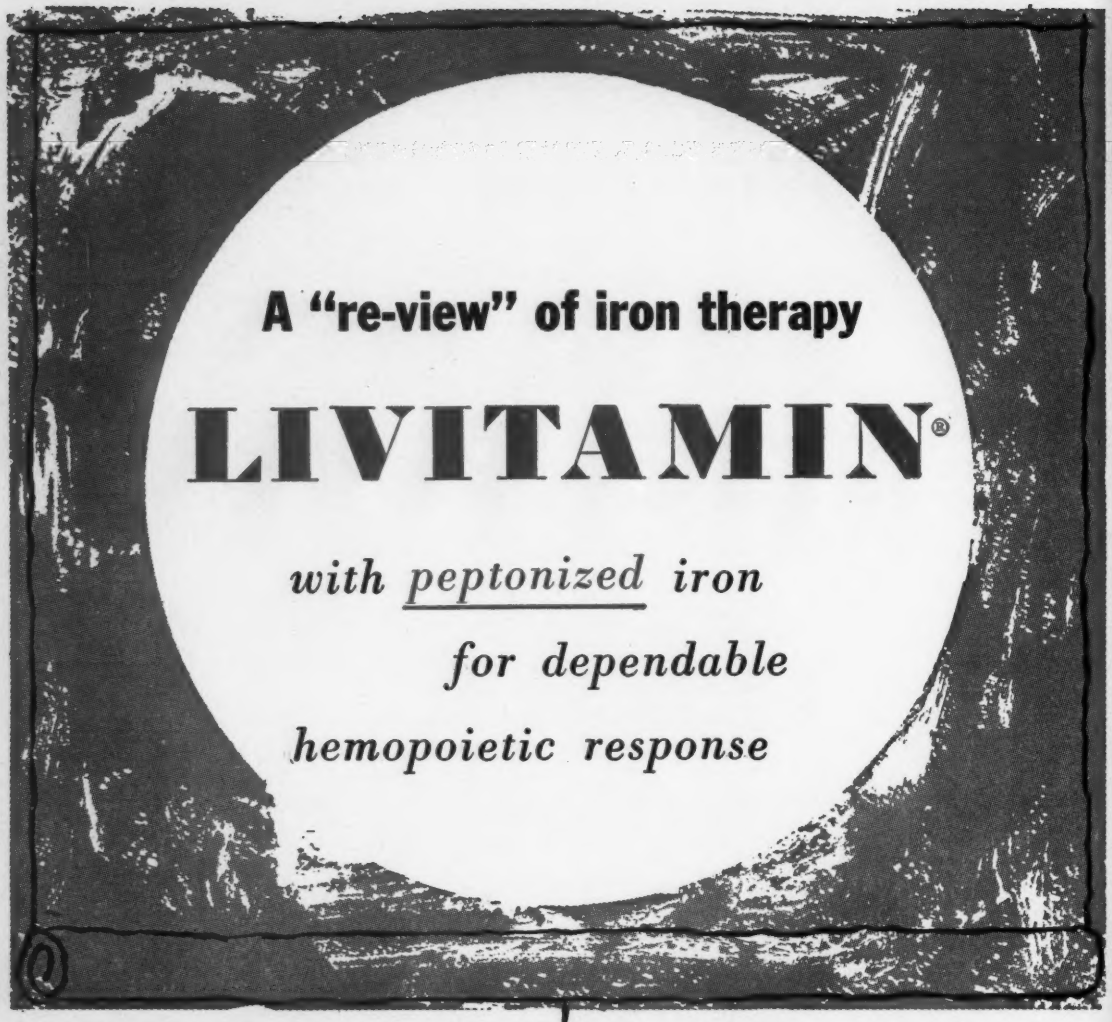

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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate. Read before the American Association for the Advancement of Science, Atlanta, Georgia, December, 1955

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1. Doyle, J. C.: California Med. *71*:15 (July) 1949. • 2. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.

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1. Nulsen, R. O.: Ohio State M.J. (In press).

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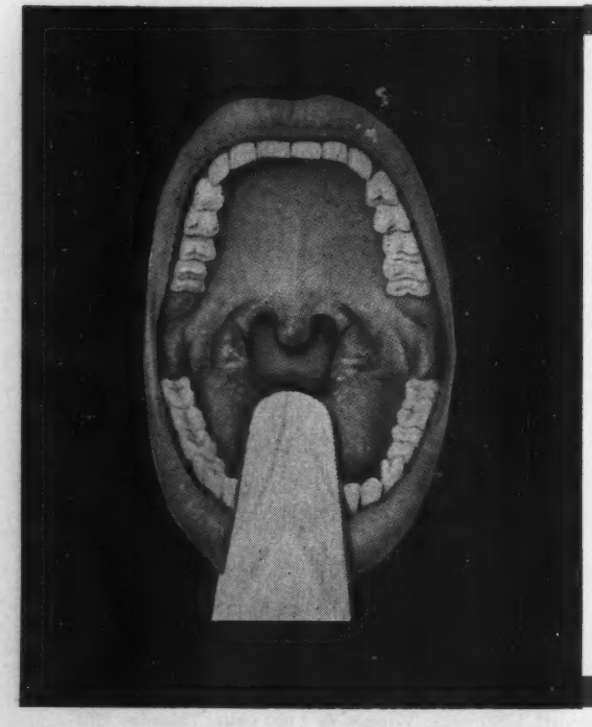

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1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51.

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1. Bacala, J.C.: The Use of the Systemic Hemostat, Carbazochrome Salicylate, West. J. Surg. *64*:88 (Jan., 1956)

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Sherber, D.A.: The Control of Bleeding, Am. J. Surg. *86*:331 (Sept., 1953)

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Peele, J.C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat, A.M.A. Arch. of Otolaryng. *61*:450 (April, 1955)

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Owings, Capers B.: The Control of Postoperative Bleeding with Adrenosem, Laryngoscope *55*:21 (Jan., 1955)

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Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. *55*:886 (Mar., 1956)

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Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. *6*:617 (June, 1955)

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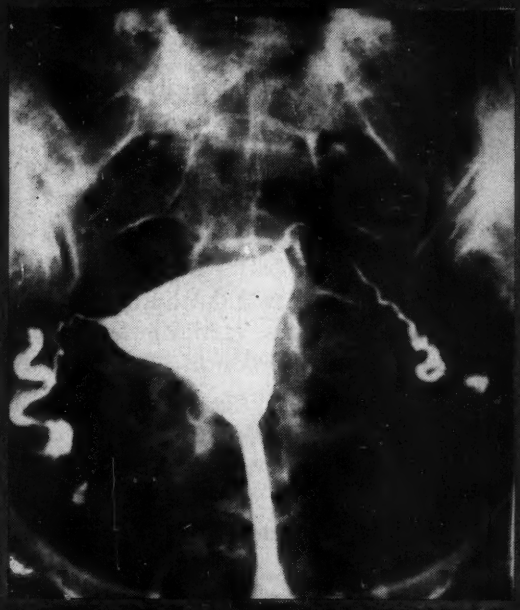

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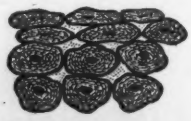
2. decreased metabolism can also originate, according to current theory, in the peripheral tissues at the cellular level (metabolic insufficiency†):

According to this theory, thyroxine, the circulating thyroid hormone, must be converted to L-triiodothyronine—apparently the ultimately active thyroid hormone—to be effective at the cellular level. If the L-triiodothyronine is not available to the cells to exert its metabolic effect, a decrease in cellular function results.

In hypometabolism due to faulty cellular utilization of the thyroid hormone (metabolic insufficiency), 'Cytomel' is the only agent now available that will produce an optimal clinical response.

†Other terms used synonymously in the recent literature are "euthyroid hypometabolism," "non-myxedematous hypometabolism," "pseudohypothyroidism" and "hypometabolic syndrome."



Cytomel* 5 mcg. & 25 mcg. (scored) tablets

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for liothyronine (L-triiodothyronine), S.K.F.

Even stubborn trichomoniasis yields... because Tricofuron is effective during menstruation, the critical time for therapy.

TRICOFURON®

Recurrences of trichomoniasis "are most likely to follow the menstrual period."[1]

"Over and over again today patients are seen with what is said to be an intractable, treatment-resistant Trichomonas infestation, but history-taking often reveals that such patients have never had treatment prescribed during any menstrual period."[2]

Menstrual blood in the vagina "forms an excellent medium for the rapid multiplication of T. vaginalis"[3] and "lowers the acidity of the vagina and hence there is a tendency to recrudescence [of trichomoniasis] at that time."[4]

Tricofuron is powerfully trichomonacidal "even in the presence of vaginal debris and menstrual blood."[3]

For 44 of 48 patients: lasting cure was obtained with a single course of Tricofuron therapy.[3]

Vaginal Suppositories—for home use—each morning and night through one cycle, including the important menstrual days. Contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base. Box of 12, each sealed in green foil.

Vaginal Powder—for office use—applied by the physician at least once a week, except during menstruation. Contains 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

References: 1. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations and Discharges, New York, The Blakiston Company, Inc., 1953, p. 235. 2. Overstreet, E. W.: Arizona M. 10:383, 1953. 3. Schwartz, J.: Obst. Gyn., N. Y. 7:312, 1956. 4. Crossen, R. J.: Diseases of Women, St. Louis, The C. V. Mosby Company, 1953, p. 292.

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Nitrofurans—a new class of antimicrobials—neither antibiotics nor sulfonamides

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BIOPAR® FORTÉ
TABLETS
• contain non-inhibitory intrinsic factor . . .
• permit optimal absorption of vitamin B_{12} at therapeutic dosage levels . . . orally

Biopar Forté Tablets contain the non-inhibitory intrinsic factor which is superior to ordinary intrinsic factor preparations. Biopar Forté provides the same rapid and intensive hemopoietic response as that obtained from injectable vitamin B_{12}. And due to the non-inhibitory intrinsic factor, this response is just as dependable.

Each Biopar Forté Tablet contains:
Vitamin B_{12} with Intrinsic Factor ½ U.S.P. Unit (Oral)*
Vitamin B_{12} (activity equivalent) 25 mcg.
Bottles of 30 tablets

*Unitage established prior to compounding

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A DIVISION OF ARMOUR AND COMPANY, KANKAKEE, ILLINOIS

eliminate pain...while maintaining muscle relaxation and patient cooperation . . . **in obstetrical delivery**

Saddle block with Heavy Solution Nupercaine, testified safe by hundreds of thousands of successful deliveries, fulfills the criteria for ideal obstetrical anesthesia: "*1. An anesthetic that is safe for both mother and baby. 2. An anesthetic that is easy to administer, and one in which personnel can be quickly and easily trained. 3. An anesthetic which alleviates pain of delivery for the patient while still inducing complete relaxation for the benefit of the obstetrician.*"[1]

1. Seegar, J.K.B.E., and Devlin, A.J.: Maryland M.J. 5:330 (June) 1956.

Supplied: 1:400 Nupercaine hydrochloride in 5% dextrose, 2-ml. ampuls, each ml. containing 2.5 mg. Nupercaine and 50 mg. dextrose; cartons of 10.

HEAVY SOLUTION **Nupercaine®**
hydrochloride
(dibucaine hydrochloride with dextrose 5% CIBA)

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Nipple fissures

Pruritus vulvae

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You'll like it and so will the patient

Tashan Cream soothes, softens, stimulates healing– contains vitamins A, D, E, and *d*-panthenol in a non-sensitizing, cosmetically pleasing, absorptive cream base.
In tubes, 1 oz.

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there's no juice like citrus juice

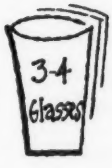
as a high-potency source of vitamin C, citrus juice is unmatched in convenience and economy

Vitamin C recommendations for peak intakes

of adolescence or pregnancy

(100 mg. per day)* are supplied by (7-9 fl. oz.)

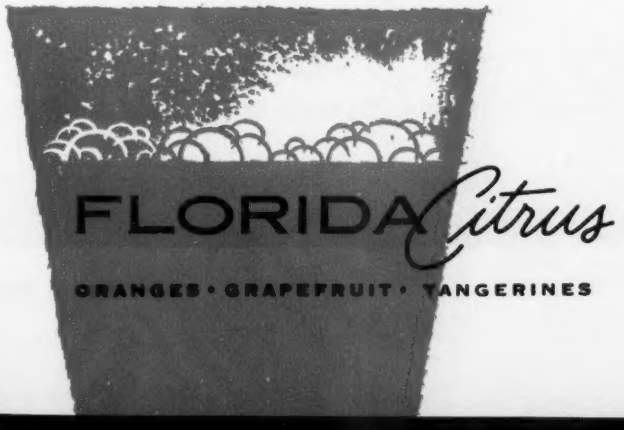
of citrus juice. But it takes of apple juice, or

of grape juice, or  of pineapple juice, or

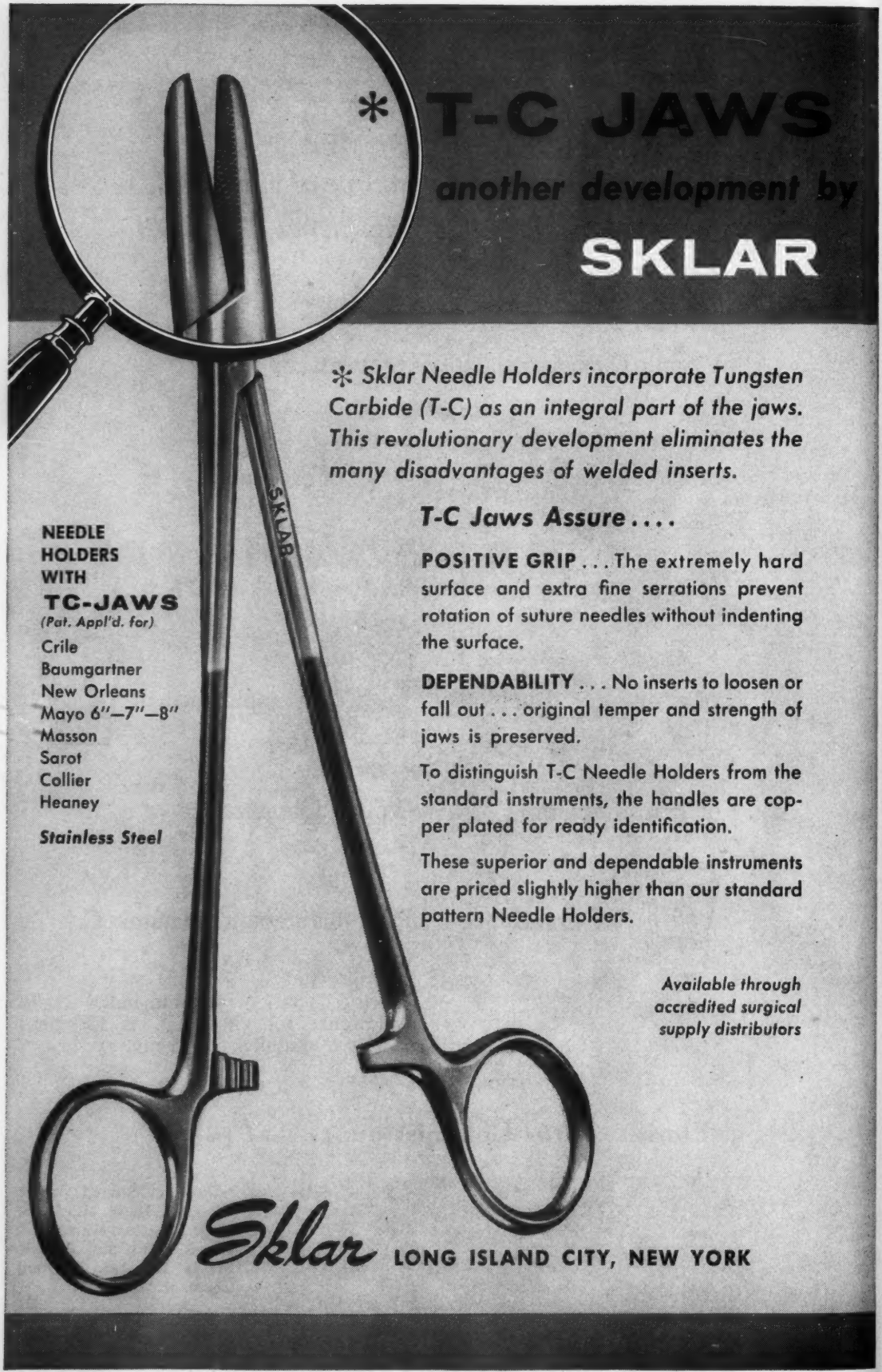
of prune juice to supply this amount of vitamin C.†

* During lactation Recommended Daily Allowance for vitamin C is 150 mg.; for normal adults, 70-75 mg.

Florida Citrus Commission, *Lakeland, Florida*



† Data calculated from: Watt, B. K. et al., U. S. Dept. Agric. Handbook No. 8, 1950; and Burger, M. et al., Agr. & Food Chem. 4:418, 1956.



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another development by SKLAR

* *Sklar Needle Holders incorporate Tungsten Carbide (T-C) as an integral part of the jaws. This revolutionary development eliminates the many disadvantages of welded inserts.*

NEEDLE HOLDERS WITH TC-JAWS
(Pat. Appl'd. for)
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POSITIVE GRIP . . . The extremely hard surface and extra fine serrations prevent rotation of suture needles without indenting the surface.

DEPENDABILITY . . . No inserts to loosen or fall out . . . original temper and strength of jaws is preserved.

To distinguish T-C Needle Holders from the standard instruments, the handles are copper plated for ready identification.

These superior and dependable instruments are priced slightly higher than our standard pattern Needle Holders.

Available through accredited surgical supply distributors

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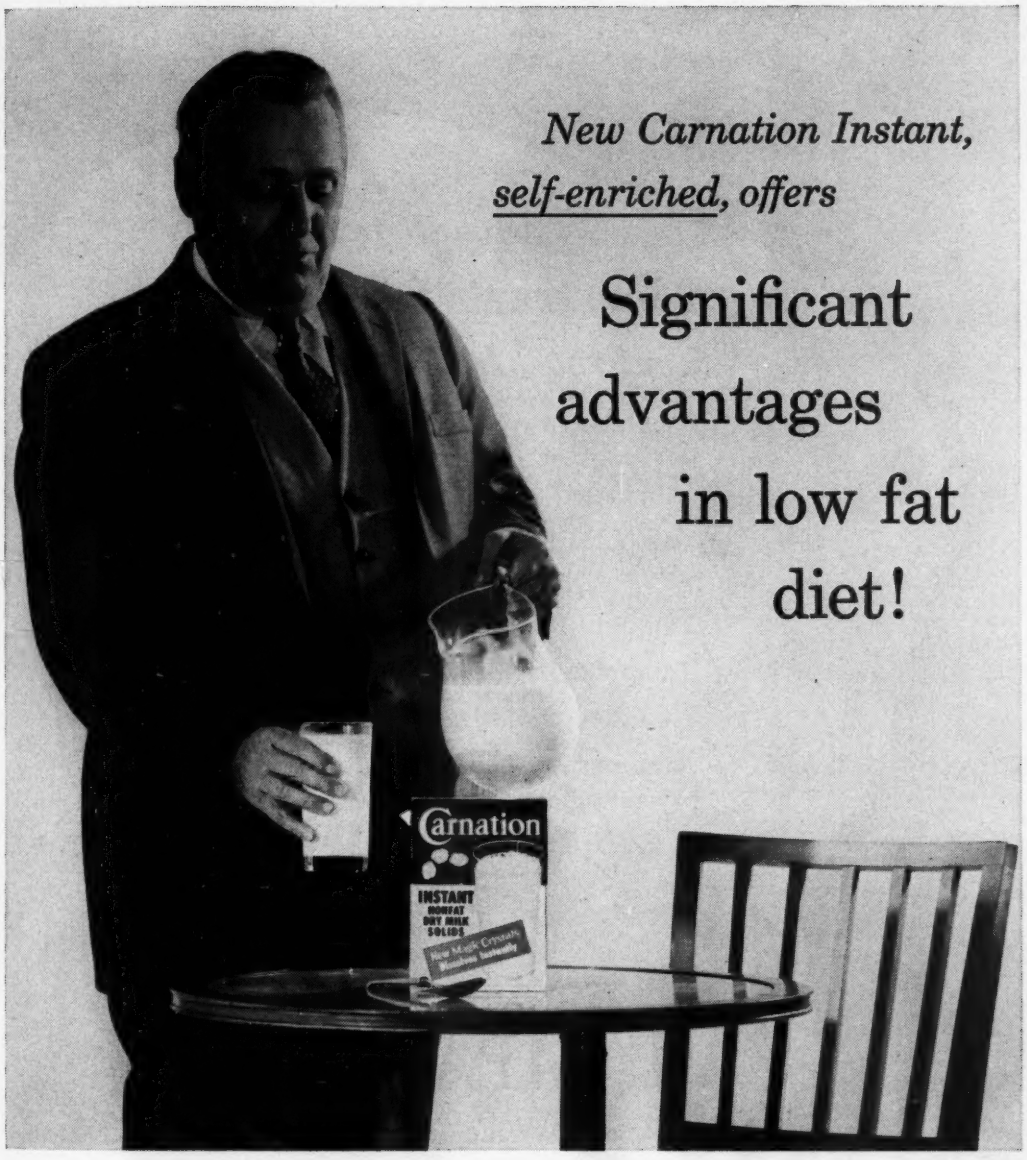


New Carnation Instant, self-enriched, offers

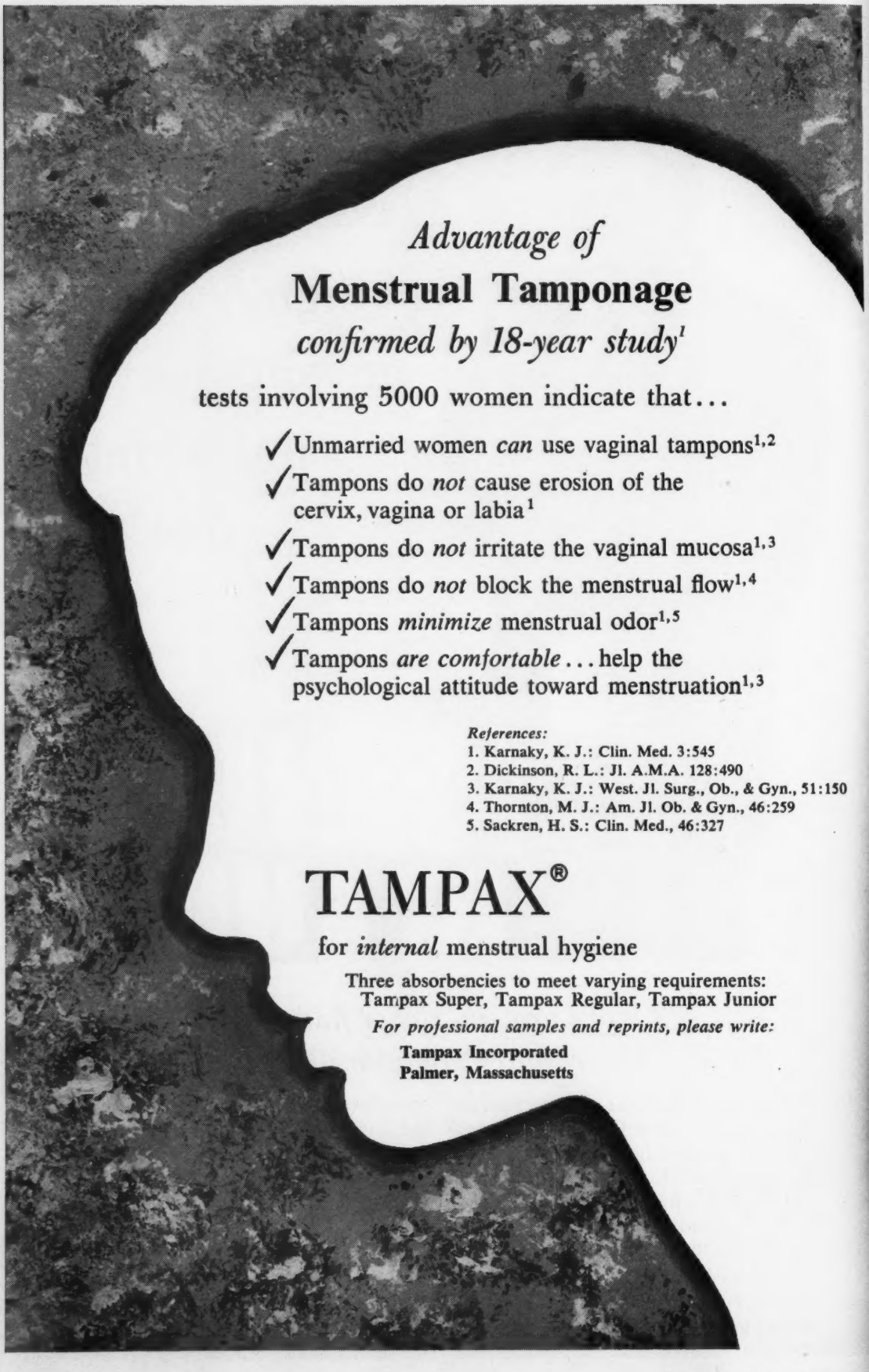
Significant advantages in low fat diet!

1/4 more protein, richer flavor than ordinary nonfat milk!

Carnation Instant, new *crystal form* of nonfat milk brings a *new* dietary advantage – delicious *self-enriched* nonfat milk. One extra tablespoon per glass, or ⅓ cup *extra* crystals per quart, provides richer flavor and significant nutritional advantages compared to the usual nonfat milk.

CONVENIENT. Mixes instantly and completely in ice-cold water with a light stir. Ready to drink, at home or away from home, with delicious fresh flavor.

MORE PROTEIN. Self-enriched Carnation Instant provides ¼ more milk minerals, B-vitamins and protein than ordinary nonfat milk – actually 41.3 grams of essential protein per quart.



Advantage of

Menstrual Tamponage

confirmed by 18-year study[1]

tests involving 5000 women indicate that...

- ✓Unmarried women *can* use vaginal tampons[1,2]
- ✓Tampons do *not* cause erosion of the cervix, vagina or labia[1]
- ✓Tampons do *not* irritate the vaginal mucosa[1,3]
- ✓Tampons do *not* block the menstrual flow[1,4]
- ✓Tampons *minimize* menstrual odor[1,5]
- ✓Tampons *are comfortable*... help the psychological attitude toward menstruation[1,3]

References:

1. Karnaky, K. J.: Clin. Med. 3:545
2. Dickinson, R. L.: Jl. A.M.A. 128:490
3. Karnaky, K. J.: West. Jl. Surg., Ob., & Gyn., 51:150
4. Thornton, M. J.: Am. Jl. Ob. & Gyn., 46:259
5. Sackren, H. S.: Clin. Med., 46:327

TAMPAX®

for *internal* menstrual hygiene

Three absorbencies to meet varying requirements:
Tampax Super, Tampax Regular, Tampax Junior

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Tampax Incorporated
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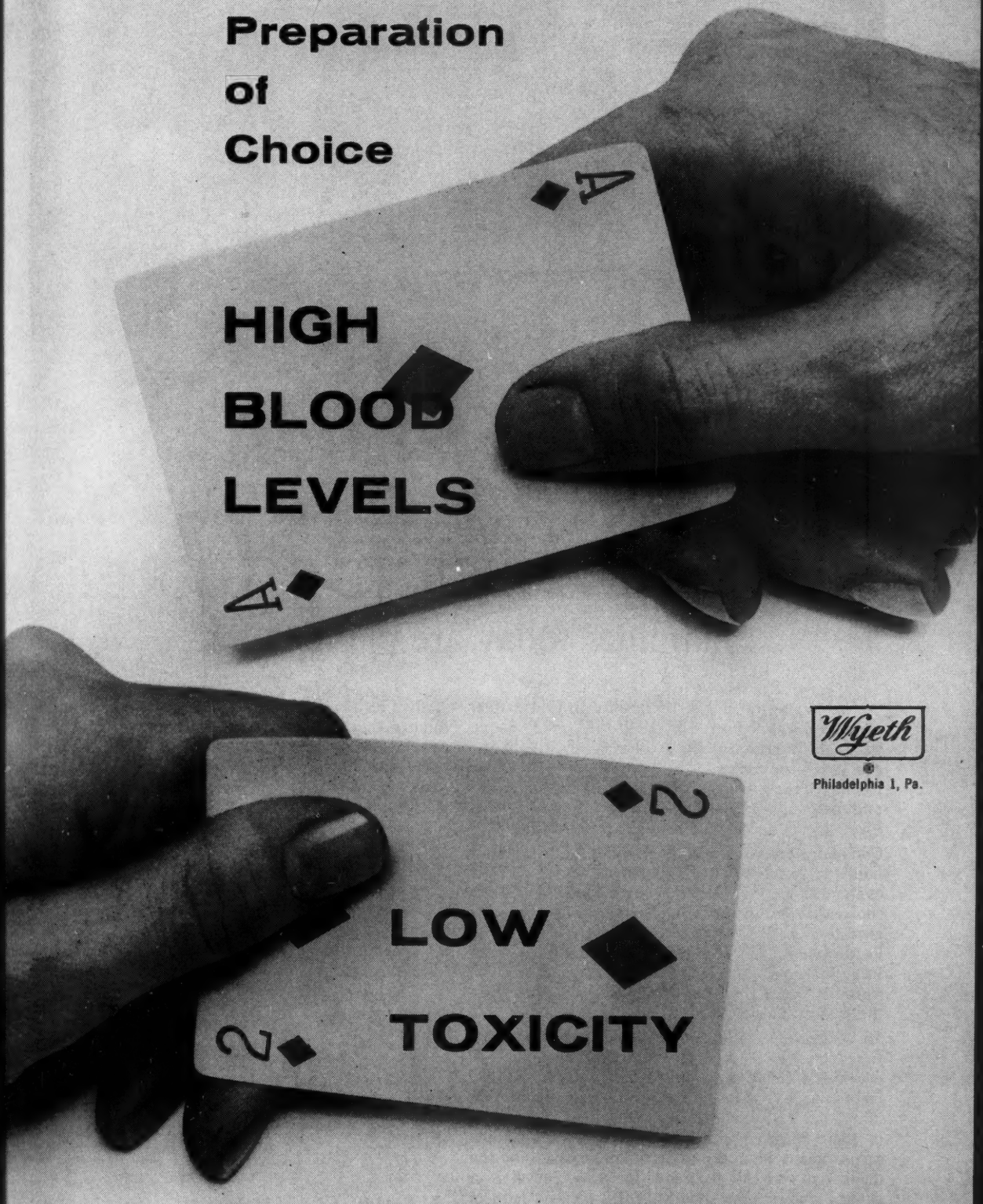
In Urinary-Tract Infections

Preparation of Choice



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SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides
(Sulfadiazine, Sulfamerazine, Sulfamethazine)

NO RACE SUICIDE HERE:

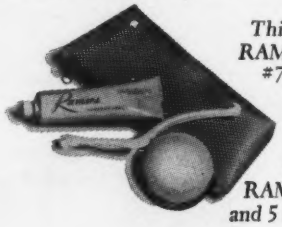
families today are planned big

"THE BIG NEWS in human fertility in mid-century America has been the 1940-1955 baby boom, which in dramatic significance has rivaled the hydrogen bomb explosions . . . ."[1] More young wives are having babies and *planning* their families big. The rate for third and fourth births has almost doubled. Five-, six- and seven-child families are on the increase.[2]

College graduates want big families — It isn't only industrial families that are growing. A survey recently completed among 29,494 graduates of 178 colleges shows that the men of the class of '45 have families averaging 70% larger than those of the class of '36 in the ten years after graduation.[3] When their wives seek advice to space their children, they want to be sure that the method recommended really gives them the protection they need.

Most effective method for women of high parity— Based on widest experience, parenthood clinics all over the world have adopted the diaphragm and jelly technique "... as possessing the least degree of fallibility . . . ."[4] *It is the preferred method for women of high fertility.* When used correctly, unplanned pregnancies seldom occur. In urban groups using the diaphragm and jelly technique for years, as well as in clinical studies, data show that this method reduces "the likelihood of conception by at least 98 per cent."[5]

Comfort helps win cooperation — Besides peace of mind, the physician assures comfort for the patient when he recommends RAMSES® Diaphragm and Jelly. Flexible in all planes, the RAMSES Diaphragm allows complete freedom of movement. Its cushioned rim avoids irritation. RAMSES "ten-hour" Jelly,* used with the diaphragm, quickly immobilizes sperm and maintains full effectiveness for up to ten hours. Patients feel confident that they have received sound contraceptive advice when physicians prescribe RAMSES protection, a critical aid in family planning for more than 30 years.



This is the attractive, complete RAMSES "TUK-A-WAY"® Kit #701 that most women prefer. Supplied in neat zippered bag with introducer and diaphragm in sizes 50 to 95 mm., and 3 oz. tube of RAMSES Jelly. Jelly refills in 3 and 5 oz. tubes. At all pharmacies.

References: 1. Dinkel, R. M.: Eugenics Quart. *3*:22 (Mar.) 1956. 2. Grove, R. D.: Am. J. Pub. Health *46*:592 (May) 1956. 3. College Study Report: Population Bulletin *11*:45 (June) 1955. 4. Novak, E., and Novak, E. R.: Textbook of Gynecology, Baltimore, The Williams & Wilkins Company, 1956. 5. Tietze, C.: Proc. 3rd Internat. Conf. Planned Parenthood, 1953.

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*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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American-MacEachern

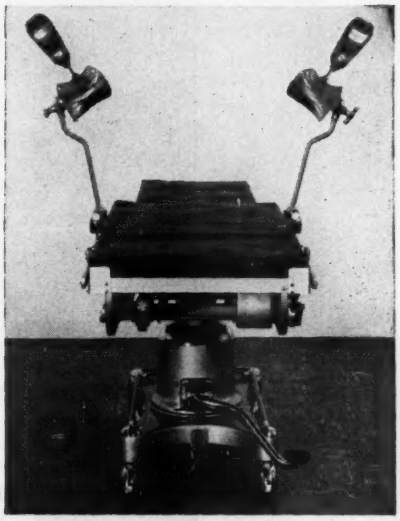
22" Operative Delivery Table.....

FOR ABDOMINAL OR PERINEAL ROUTE DELIVERY

• The new 22" **500N** table assures both the patient and the Obstetrician the fullest advantages of modern obstetrical practice under *all* conditions.

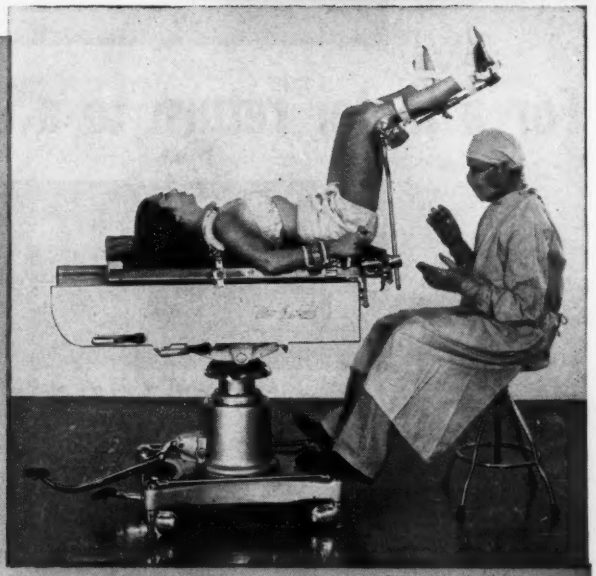
The growing practice of performing cesarian sections in the O. B. room . . . without moving or disturbing the patient . . . is made easy by the 22" surgery width of the **500N.** Yet the table will accommodate even the largest patient during normal delivery and the universally adjustable knee and foot rests accommodate all patients fron the tallest to the shortest.

Write for our new Obstetrical Table Catalog C-124-R



The "clean" lines of the 500N table provide maximum comfort and freedom for the surgeon . . . with toe space, folding handles, etc.

If non-elective cesarian section is indicated, patient is quickly and easily positioned for surgery simply by lowering extremities and raising the foot section. The anesthetist need not change position of head of patient.



15" height adjustment and every known obstetrical posture from high lithotomy to Walcher position provides convenient approach to the perineal field.

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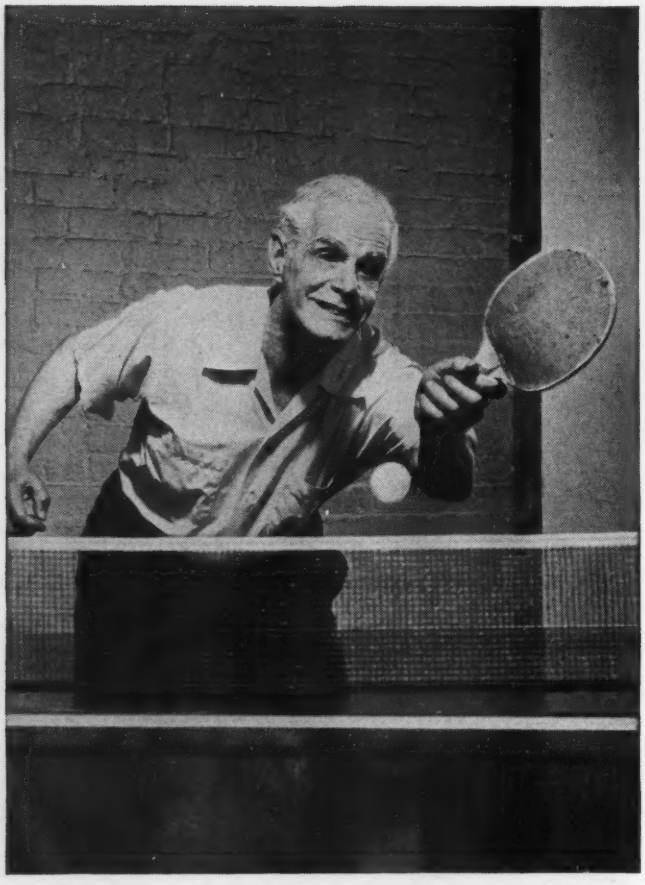
BRANCH OFFICES IN 14 PRINCIPAL CITIES



For a faster return to a bright blood picture

REDITRIN-T

HIGH POTENCY HEMATINIC WITH INTRINSIC FACTOR AND MINERALS

All treatable anemias will respond to potent REDITRIN-T. One capsule daily supplies all the known agents of blood regeneration—including Vitamin B_{12}, intrinsic factor, folic acid, ferrous sulfate. Ascorbic acid keeps iron in the absorbable ferrous state, and trace elements act as catalysts to speed regeneration of red cells.

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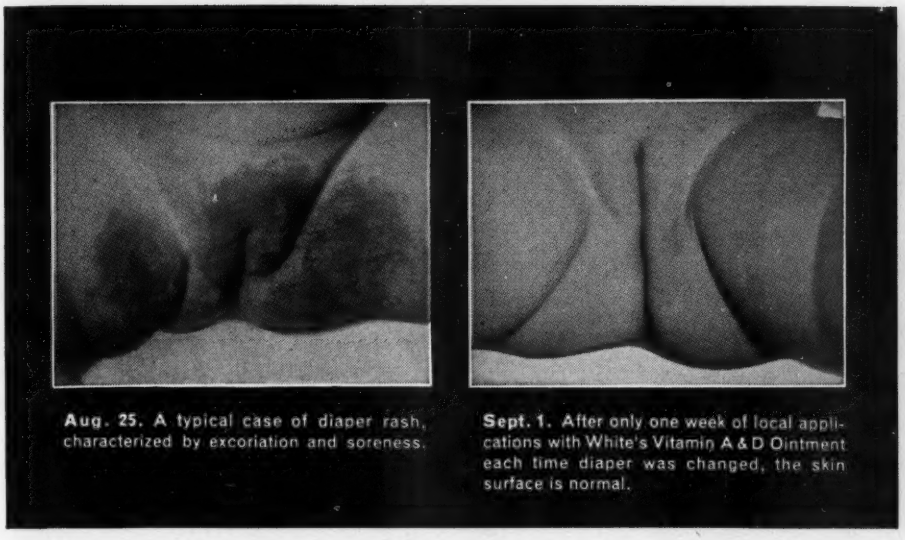

Aug. 25. A typical case of diaper rash, characterized by excoriation and soreness.

Sept. 1. After only one week of local applications with White's Vitamin A & D Ointment each time diaper was changed, the skin surface is normal.

it's becoming routine therapy

particularly in

prevention and treatment of diaper rash

and in many other common skin conditions: burns, cuts, sunburn, chafing, prickly heat, chapping, cracked nipples

White's Vitamin A & D Ointment

it's healing...soothing...protective.

Provides A & D vitamins in the same ratio as found in cod liver oil.

KEEP A TUBE OF THE NEW
ECONOMICAL 4 OZ. SIZE
HANDY FOR EMERGENCIES
AND ROUTINE SKIN CARE

WHITE LABORATORIES, INC.
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for the modern woman...a modern prenatal supplement

Today's pregnant woman is more fortunate than her sister of yesteryear . . . she looks better, feels better and enjoys greater freedom during her pregnancy. She is free, too, from such traditional prenatal distress as leg cramps, irritability and mild edema when a *modern* prenatal supplement is prescribed.

Usable calcium—Recent evidence points to a new rationale of prenatal nutrition. ". . . it is apparent that dicalcium phosphate, so widely used as a dietary supplement in pregnancy, is undesirable."* Calcisalin, for routine prenatal supplementation, provides calcium in the *usable* form of the lactate salt, rather than phosphate.

The complete prenatal supplement – Calcisalin also provides reactive aluminum hydroxide gel (to absorb excess dietary phosphorus) and the minimum daily vitamin and iron allowances for pregnancy as recommended by the National Research Council.

Thus the risk of inadvertently raising the phosphorus level to the point where it interferes with calcium absorption is avoided with Calcisalin.

Dosage: Two tablets three times daily after meals. *Available:* Bottles of 100 tablets and 8-oz. reusable nursing bottles containing 300 tablets.

*Page, E. W., and Page, E. P.: Obstet. & Gynec. *1*:94 (Jan.) 1953.

Calcisalin®

WARNER-CHILCOTT

IN VAGINAL TRICHOMONIASIS—

EXPLODE TRICHOMONADS

WITH VAGISEC® *liquid and jelly*

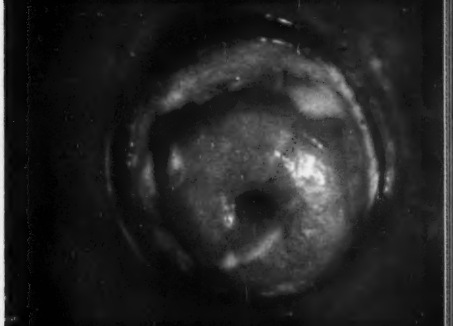
FOR GREATER TREATMENT SUCCESS—

FEWER RECURRENCES

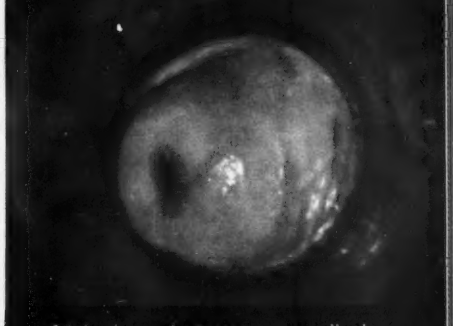
Here at last is a uniquely effective treatment[1-4] that rids patients of vaginal trichomonads successfully in more than 90 per cent of cases without long-term therapy.[3] VAGISEC liquid and jelly even clear up long-standing infections,* often in less than a week. Marked improvement is usually seen within the first 24 hours. And here's why.

Both VAGISEC liquid and jelly explode trichomonads in 15 seconds after contact.[1,3-5] 'Round-the-clock therapy with liquid and jelly, the Davis technique,† explodes—not merely inactivates—hidden trichomonads as well as those easily reached. This controls the infection immediately and keeps it under control until the last trichomonad explodes and disappears, as these photographs taken before, during and after VAGISEC treatment so clearly show.

Cervix of patient with severe *Trichomonas vaginalis* infection as seen after exposure with a speculum. Note the reddened mucosa, copious secretion, and "strawberry" appearance which is often seen in acute cases.



2nd day—After one office treatment with VAGISEC liquid and liquid and jelly at home, note regression of inflammation, markedly less discharge. (Burning, itching, and most of the soreness are gone.)



28th day—Apparent "cure" shows intact mucosa, and normal secretion (microscopically negative for trichomonads) after 3 days without therapy following menstruation. (Results confirmed by check-up 3 months later.)

*A small percentage of women who have an involvement of the cervical, vestibular or urethral glands may require other types of treatment.[1,3,4]

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Boric acid, Alcohol 5% by weight.

PLEASE TURN PAGE

VAGISEC® *liquid and jelly*

"I have been impressed by this method of therapy and by the results in my own private patients."[2]

CONSIDER THE HUSBAND

Many re-infections occur in patients successfully treated for vaginal trichomoniasis, or the infection proves refractory because the husband, although asymptomatic, is a source of trichomonads.[1-3,7,8] "The presence of trichomonads in the male genitourinary tract should always be suspected in the husband of a woman who is repeatedly reinfected."[7]

To prevent the husband's re-infecting the patient, leading authorities agree that prophylactics for the husband are indicated as part of the treatment plan[1,3,7-9] during the wife's treatment course and "... permanently if he carries the infection."[3] Karnaky recommends: "In resistant and recurring cases ... the husband should wear a condom at coitus for four to nine months, during which time these trichomonads will usually die out on their own accord."[8]

Most doctors routinely advise this regimen but the problem remains of ge[illegible] low this advice. W[illegible] prophylacti[illegible]

References: 1. Davis, C. H. (Ed.): Gynecology and Obst[illegible] (revision), Hagerstown, W. F. Prior, 1955, vol. 3, chap. 7, 23-33. 2. McGoogan, L. S.: J. Michigan M. Soc. *55*:682 ([illegible] 1956. 3. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 195[illegible] Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955. 5. Molomut[illegible] Port Washington, N.Y.: Personal communication (June) [illegible] 6. Davis, C. H., and Grand, C. G.: Am. J. Obst. & G[illegible] *68*:559 (Aug.) 1954. 7. Draper, J. W.: Internat. Rec. [illegible] *168*:563 (Sept.) 1955. 8. Karnaky, K. J.: J.A.M.A. *15*[illegible] (June 26) 1954. 9. Bernstine, J. B., and Rakoff, A. E.: V[illegible] Infections, Infestations and Discharges, New York, The [illegible] ton Co., 1953.

The protection RAMSES prophylactics af[illegible] is the very foundation of re-infection[illegible] Prescribe this prot[illegible] nine

Prescribe the one with "built-in" sensitivity

Husbands will cooperate better in vaginal re-infection control if you prescribe RAMSES,® the superior rubber prophylactic. Transparent, smooth, tissue-thin, yet strong, RAMSES are the prophylactics most men know and prefer. Show your thoughtfulness by writing a prescription for RAMSES that the patient or her husband can hand to the druggist, or offer to phone the druggist yourself.

RAMSES®
prophylactics

"One should not fo[illegible] that re-infections [illegible] occur and they ca[illegible] from her husband

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423 West 55th Street, New York 19, N. Y.

VAGISEC and RAMSES are registered trade-marks of Julius Schmid, Inc.
†Pat. app. for

control nausea
and vomiting
of pregnancy
RECTALLY

ANTINAUSEA

SUPPRETTES®

- Provide prompt relief from nausea and vomiting
- One Supprette inserted rectally before arising usually suffices
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- Complete utilization of medication assured
- Synergistic combination of drugs enhances efficacy
- No discomfort, irritation or leak-back
- Helps pregnant women enjoy pregnancy

Supplied:
Antinausea Supprettes

No. 1 (pyrilamine maleate 50 mg., pentobarbital sodium ¾ gr.).

No. 2 (pyrilamine maleate 50 mg., pentobarbital sodium 1½ gr.).

In jars of 12.

The "Neocera" Base Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes readily with rectal fluids.

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SUPPRETTE/SUCCESSOR TO THE SUPPOSITORY

No Refrigeration Necessary—Samples on Request

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GREATER FULFILLMENT

OF THE DESIRABLE EFFECTS

OF THIOBARBITURATE ANESTHESIA

Schering

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ng intravenous anesthetic

YOU CAN CONFIRM THESE CLINICAL EXPERIENCES

- Significantly faster detoxification and elimination than either thiopental or thiamylal[1,2]
- Shorter duration of action[1]
- Considerably less accumulation[3,4,6]
- More rapid, complete recovery[3,5-7]
- Strikingly rapid awakening[1,3,5]
- Better moment-to-moment control[3]
- Less postoperative supervision[1]
- Fewer postanesthetic side effects[3,7,8]

Clinical findings such as these suggest an early trial with NERAVAL.

NOTE: Lower milligram potency and more rapid detoxification of NERAVAL compared with thiopental and thiamylal provide greater clinical safety and better moment-to-moment control. For equivalent anesthetic effect approximately 1½ to 2 times as much NERAVAL is usually required.

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IN INTRAVENOUS ANESTHESIA

Neraval
SODIUM

"... the shortest-acting thiobarbiturate so far known to us ..."[1]

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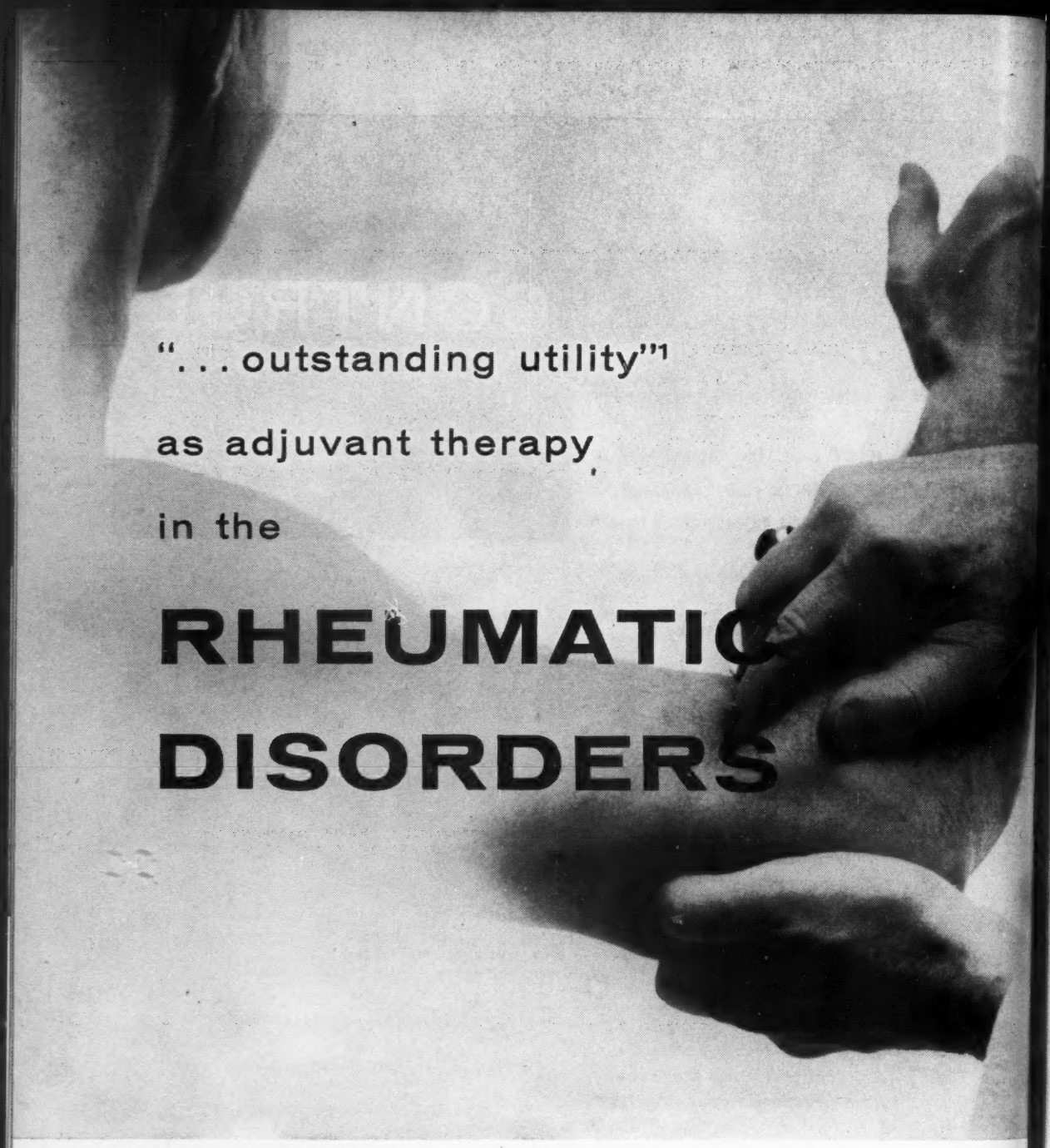

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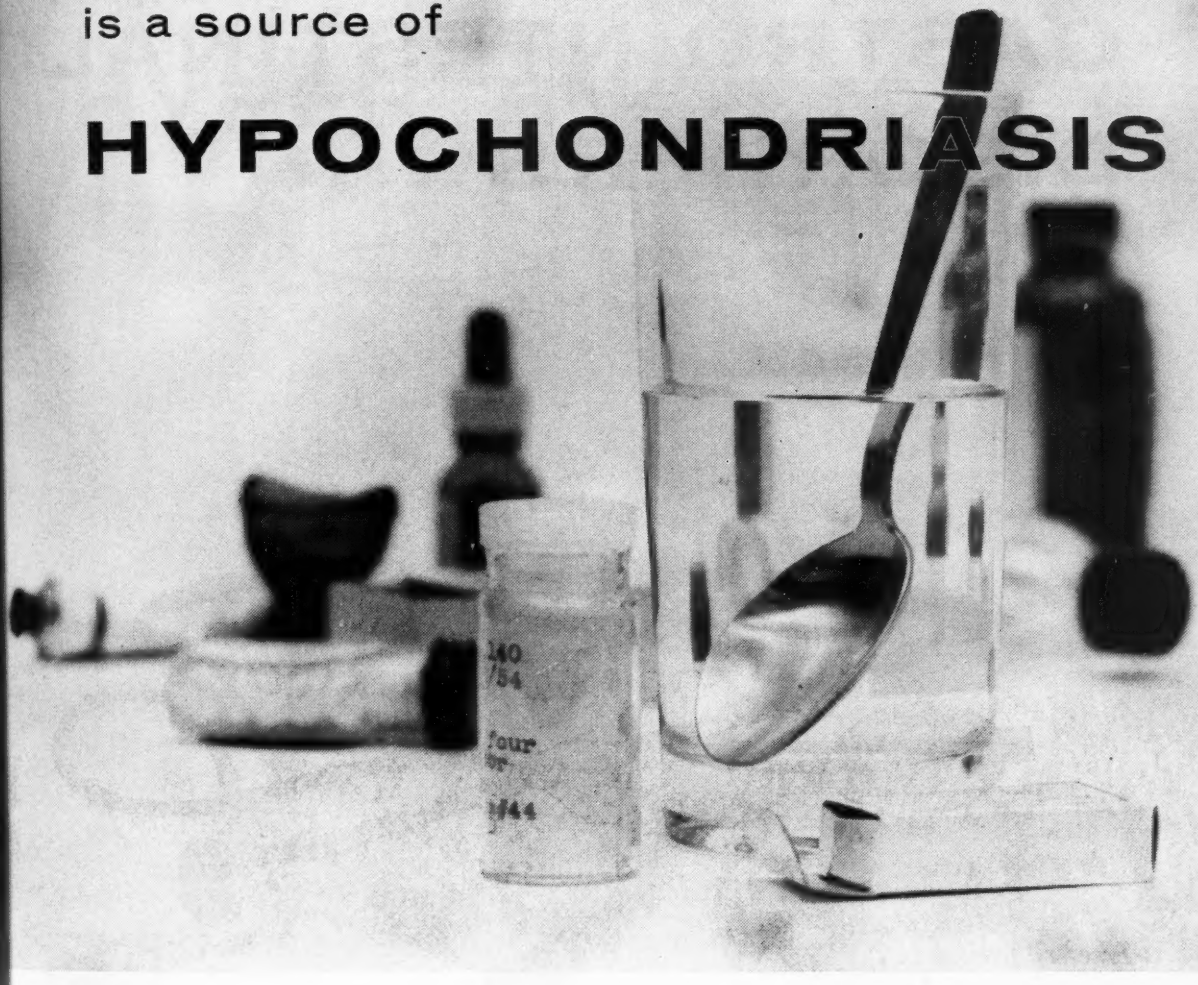

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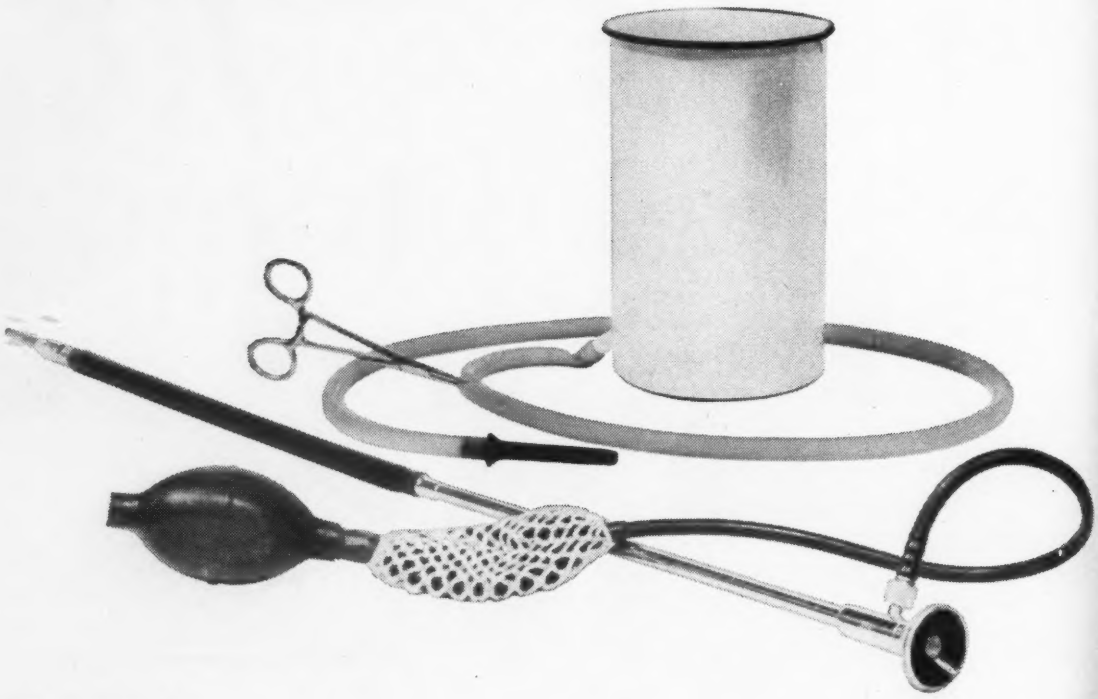

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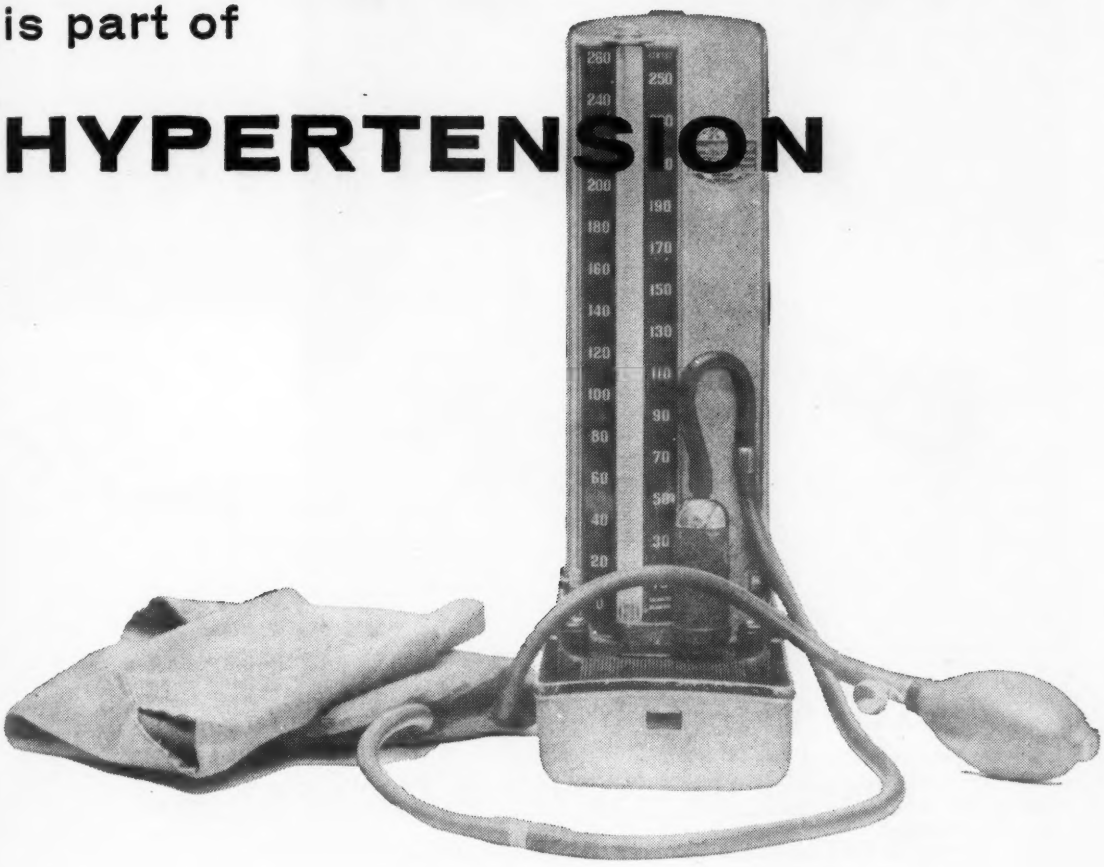

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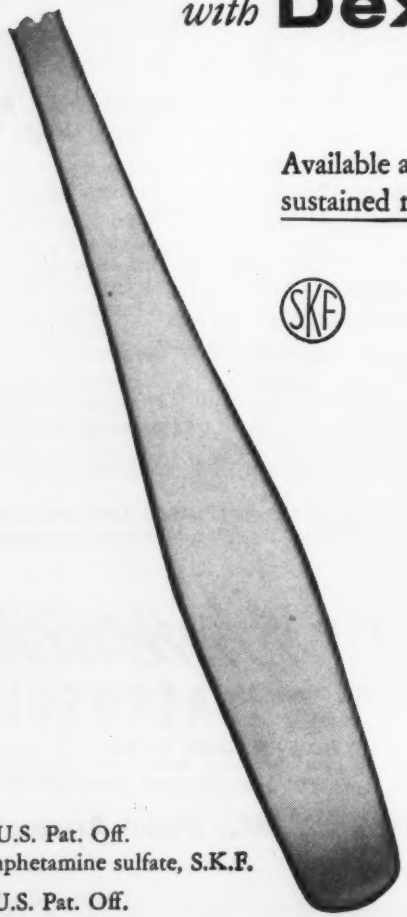

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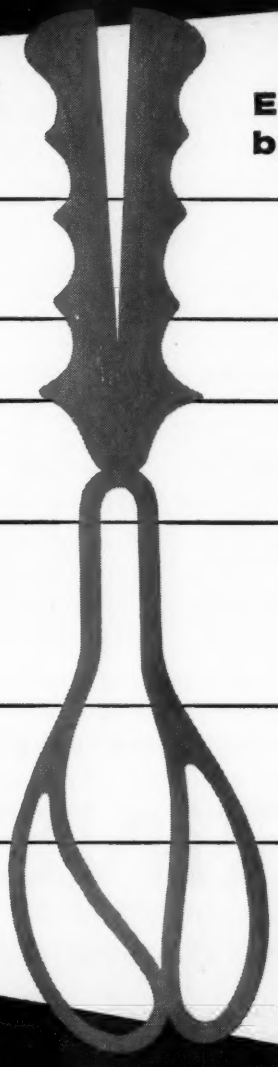

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Obstetrics

SHOCK IN OBSTETRICS*

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(From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital)

SHOCK is a continuing and sinister hazard to the pregnant woman. Despite the commendable reduction in maternal mortality in recent years, deaths from this cause have not decreased proportionately. Indeed, in some sections of the country shock has become the leading cause of maternal death, while shock from blood loss is often a major factor in obstetrical deaths assigned to other causes. Furthermore, the most serious sequelae of pregnancy, namely, damage to the adenohypophysis and kidney, are related consequences of shock.

Admittedly, for a number of reasons, it is a more difficult task to eliminate deaths from shock and hemorrhage than from other obstetrical causes. While there may be a degree of urgency, obstetrical complications other than shock rarely need be classified as emergencies. Indeed, patients with toxemia, failed labor, or medical disease complicating pregnancy can always receive the benefit of consultation and, if necessary, without additional risk may be transferred considerable distances to a hospital better prepared to care for them. Patients who develop shock demand immediate and vigorous treatment by the personnel present using the facilities at hand. Ignoring for the moment such matters as foresight, judgment, and technical competence as they relate to the problem of shock in obstetrics, the physician is often confronted with the condition without warning. Only too frequently he may not have adequate help and facilities for treating a patient with shock.

In other words, much of the responsibility for deaths from shock in obstetrics rests with the hospital as well as the physician. Commenting lucidly on the subject of the challenge of reducing maternal mortality, Taylor[45] has

*The Rudolph Weiser Holmes Lecture on Maternal Welfare, presented at a meeting of the Chicago Gynecological Society, March 16, 1956.

recently asked some pertinent and pointed questions: "Are the necessary safeguards available to care for the obstetrical patient, and do all hospitals warrant the confidence in them by the public? Is suitable blood available on the delivery floor, and in adequate amounts?"

While the profession and health authorities should question the adequacy of some hospitals to care for obstetrical patients, it is equally important to ask whether in obstetrical situations where shock is a threat the procedure and policies of management are entirely correct. When the record is reviewed, it is apparent that there is much which can be done to prevent deaths from this cause.

The purpose of this paper, therefore, is to inquire into the various forms of shock encountered in the obstetrical patient, the factors which contribute to it as well as the reasons for therapeutic failure, and to express some personal views about prevention and treatment. Only some of the more controversial aspects of the problem will be considered, for in its totality shock touches on many phases of obstetric practice. This report is concerned largely with the clinical features of shock, for there are readily available several complete symposia which review the current views on shock.[9, 14, 43, 51]

When seeking to eliminate deaths from shock, it should be reiterated that the majority of women are delivered in community hospitals by physicians, many of whom are busily engaged in general practice. It must be recognized that whatever methods and procedures are advocated for the prevention and management of shock in the obstetrical patients, they must apply to the community hospital as well as to the metropolitan hospital, the latter usually with a large house staff and possessed of a sizable blood bank, albeit often a long distance from the case room.

A number of sources have provided the basis for these remarks, including a seven-year review of the maternal deaths, from 1949 to 1955, inclusive, in the Commonwealth of Massachusetts, and a comparison with similar studies from other states.[11, 24, 25, 27] A further source of references is a comparatively large group of obstetrical patients with acute renal failure cared for jointly by the Medical Service at the Peter Bent Brigham Hospital and the Obstetrical Service at the Boston Lying-in Hospital.

Definition of Shock

In this discussion, shock is defined as a syndrome characterized by a decrease in effective blood volume associated with an insufficient cardiac output leading to peripheral circulatory failure which, if uncorrected, will result in eventual progressive circulatory deterioration. Consequently, shock may be produced by either reducing the circulating blood volume, interfering with normal cardiac action, or impairing the function of the peripheral vessels themselves. Whatever mechanism is primary, the inability to compensate can result in shock.

Conventionally, shock is assigned to either (1) trauma with blood loss, (2) sepsis, or (3) myocardial infarction, and in some patients the causes are multiple. An example of an accumulation of causes is in *B. welchii* sepsis, where in addition to the toxic effect on the peripheral circulation there is often a significant reduction in effective blood volume through hemolysis.

Recently it has been suggested that the hypotensive episode which occurs while in the supine position in the occasional pregnant patient near term is shock.[19] This state has been considered recently by Sharpey-Schafer[4, 38] to be similar to the hypotension induced by spinal anesthesia, and he has designated it as a form of syncope. Certainly the peripheral pooling of blood mediated by uterine pressure on the inferior vena cava perhaps neurogenically induced does not constitute a state of deterioration similar to shock. Hamilton[17] remarked that such symptoms are readily relieved by placing the patient on her side. In contrast to shock, such prompt recovery indicates that the homeostatic mechanisms which regulate circulatory changes have not been compromised. It is conceivable, however, that in the undelivered patient who is in shock the condition may be aggravated by the supine position.

The term "obstetric shock" has been introduced to designate the circulatory change which may ensue following possible occlusion of the pulmonary-arterial system by amniotic fluid and its contents or from fibrin deposition in abruptio placentae supposedly from massive intravascular coagulation.[37, 38]

Customarily, embolic phenomena involving the pulmonary system are not included in a discussion of shock, for where death occurs it usually ensues before peripheral circulatory deterioration has time to develop. When the embolus is nonfatal, the hypotension is transient both clinically and experimentally. Initially, in the case of amniotic fluid embolism, death was attributed to dual causes, namely, anaphylaxis and occlusion of the pulmonary circulation.[41] Usually the mechanism of death is indistinguishable from that of pulmonary embolism. In this instance, however, should the patient survive the initial embolic insult she may ultimately succumb from hemorrhagic shock. From a proved case of amniotic fluid embolism where the patient died from uncontrolled hemorrhage associated with the inability of the blood to clot, this defect was postulated to be due to fibrinogen depletion.[50] Subsequent observations have indicated that this is a possibility.[30, 33] Thus the occasional case of amniotic fluid embolism with hemorrhagic sequelae could be properly included in shock. Unfortunately, most patients with amniotic fluid infusion exhibit the signs and symptoms associated with a massive pulmonary embolism and sudden death.

The following case from this series is offered to illustrate that an apparent coagulation defect may develop in a patient with amniotic fluid embolism resulting in death from hemorrhagic shock.

CASE 1.—A primigravida with an uncomplicated prenatal course entered a community hospital in spontaneous labor at term and was delivered uneventfully after an eight-hour labor. The fetal heart tones were lost two hours prior to delivery, and the cause of the stillbirth was not apparent. A second-degree laceration of the perineum was repaired under general anesthesia. The placenta separated after twenty minutes, following which the patient had persistent vaginal bleeding. According to the nurses' notes, the patient was given 1,000 c.c. of 5 per cent dextrose and saline, an additional ampule of Ergotrate and Pituitrin, and 300 c.c. of plasma. She was transferred to a metropolitan hospital and was in critical condition on arrival. Blood taken at this time failed to clot, although further studies were not made. The patient was restless, radial pulse was absent, blood pressure was unobtainable, and the patient died forthwith, some three hours and fourteen minutes after delivery. An autopsy performed by the Department of Legal Medicine at Harvard Medical School showed findings consistent with amniotic fluid embolism.

While generalized fibrin deposition is occasionally seen in patients, pregnant and nonpregnant, who die from hypertensive states, this phenomenon is rarely observed in the tissues in fatal cases of abruptio placentae. Even in

these rare instances, it is difficult to dissociate the possible presence of toxemia of pregnancy and other hypertensive conditions. If extensive fibrin deposition is a characteristic feature of severe abruptio placentae and is sufficient to cause pulmonary hypertension, one would anticipate evidence of right heart failure as delineated by cyanosis, pulmonary edema, and increased venous pressure. Clinically such findings are not seen even in the more severe forms of abruptio placentae, nor when blood is administered in large amounts to these patients in an effort to restore the blood volume to normal. It has been suggested that parenteral fluids, including blood transfusion, might be dangerous by further embarrassing the right heart in the presence of pulmonary hypertension. This has more than theoretical implications in the management of shock in obstetrics because patients who die from this cause rarely receive adequate amounts of blood.

The idea that there is a separate entity which should be designated "obstetric shock" is further engendered by statements which connote the belief that in abruptio placentae the degree of shock is out of proportion to the visible blood loss. Actually, when shock develops in cases of abruptio placentae, the degree of blood loss is extensive and in fatal cases is often not fully appreciated until autopsy reveals marked extravasation of blood throughout the retroperitoneal spaces of the pelvis and abdomen. Further, in estimating blood loss it is well to recall that the observed clot may represent no more than 40 per cent of the blood shed. Consequently, it appears that shock in abruptio placentae is the result of a significant decrease in effective blood volume from blood loss.[31]

In summary, amniotic fluid embolism is a variant of pulmonary embolism and should not be properly considered in a general discussion of shock except in the rare instance where a clotting defect develops, in which case it may be considered in the category of shock due to blood loss.

Syncope, or loss of consciousness from acute decrease of cerebral blood flow, a common symptom of pregnancy, is excluded by this definition. In other words, a hypotensive state is not synonymous with shock, for shock denotes a physiologic state in which the body, unaided, cannot compensate sufficiently to restore the blood pressure to normal. According to the definition used here, therefore, shock in obstetrics is similar in all respects to that seen in medical or surgical conditions, and the treatment of the syndrome is identical.

Clinical Features of Shock

The severity of shock is related to the degree of reduction in effective blood volume, and in the case of trauma or injury in the obstetrical patient this decrease is the result of hemorrhage rather than any loss of intravascular fluid into an area of injury. In general, when the arterial pressure falls below 100 mm. Hg, and the pulse rate increases, a forewarning of impending shock, the blood volume has already been reduced by some 30 to 35 per cent, or the equivalent of 2 L. of blood. The signs of a failing peripheral circulation soon follow with the appearance of cold, moist extremities. Should shock be extreme, the skin may become mottled, at which time the blood pressure is usually unobtainable and the radial pulse barely perceptible. Restlessness and mental confusion are prominent symptoms resulting from an oxygen deficit created by the decrease in cardiac output.

In shock due to sepsis the alteration in hemodynamics is largely unknown. The blood volume is not reduced except in cases of peritonitis with possible transudation of plasma or in Clostridium infection with destruction of red cells. The cardiac output falls, but vascular resistance fails to occur, presumably because of the effect of bacterial toxin on the peripheral vessels.

Where shock develops following myocardial infarction, while the cardiac output diminishes, there is no reduction, and at times there is an actual increase in blood volume. Effective blood volume, however, is diminished and, unless cardiac function improves, peripheral vascular deterioration ensues.

In an effort to maintain effective blood volume to the brain and myocardium in the presence of shock, vasoconstriction occurs especially in the skin and kidney. Thus, renal blood flow is markedly reduced actually out of proportion to the decrease in cardiac output. Experimentally, renal blood flow may nearly cease when the blood volume is decreased by 40 per cent, and the fact that the systolic blood pressure values often remain between 80 and 100 mm. Hg is evidence of the high degree of renal vasoconstriction present. Oliguria and anuria often follow and persist until the arterial pressure is restored and maintained at a normal level for a period of several hours.

Being younger individuals and for the most part in a state of good health, obstetrical patients can tolerate greater amounts of blood loss without exhibiting evidence of shock in contrast to the older patients in whom degenerative changes limit the capacity to compensate. Consequently, when overt shock develops in the pregnant patient, especially with repeated episodes of bleeding, she may be approaching a state of exsanguination.

While the term "irreversible" is used to describe the state of shock when the patient fails to respond to blood volume replacements, this clinical state has defied precise definition. Irreversibility or therapeutic failure is related to the amount of blood loss and the duration of shock, as well as the depth and length of anesthesia and extent of trauma. Experimentally, where the blood volume remains below 50 per cent of normal for a period longer than four hours, the response to therapy diminishes appreciably, despite its adequacy. While the subject of much study and speculation, no satisfactory explanation can be offered as to why the body loses its ability to respond to the restoration of normal blood volume. The tendency, moreover, of the body to become refractory to blood replacement in the presence of recurrent bleeding has special significance in the management of the obstetrical patient.

Material

For the years 1949 to 1955, inclusive, the maternal deaths reported in the Commonwealth of Massachusetts have been reviewed through the combined efforts of the Maternal Welfare Committee of the State Medical Society and the State Departments of Health and of Vital Statistics. During this seven-year period there were at least 306 maternal deaths, of which 84 were due to shock. It is apparent that unless these cases are sought for and reviewed in this manner the total number of deaths from the various causes will not be known accurately. This applies particularly to deaths assigned to shock and hemorrhage where the element of preventability looms large.

Similar to the experiences of surveys made in other states, it is clear that some 20 to 30 per cent of maternal deaths are not so classified and are reported as deaths due to nonobstetrical causes. These figures, therefore, are only an approximation of the total maternal mortality for this seven-year period. The inaccuracy is due in part to the misconception as to what constitutes a maternal death, a definition which unfortunately differs from state to state, as well as from country to country. In Massachusetts as in many states, there is no precise definition in the statutes, but it has been arbitrarily accepted that the death of a patient from any cause during pregnancy or within 90 days following delivery is, or should be, classified as a maternal death.

It is disturbing that many physicians and hospital administrators are not familiar with or disregard the accepted definition. This applies particularly

to the larger general hospitals where obstetrical patients with complications are sometimes transferred to other services. As the Maternal Welfare Committee in Massachusetts has gained greater perception in methodology, it is evident that the number of deaths found and reviewed exceeds significantly the number of death certificates (±25 per cent) filed with the Department of Vital Statistics of the State.

The percentage of deaths from the various obstetrical complications is influenced also by the way the mortality rate is computed. Many countries and some states subdivide maternal deaths into obstetrical and nonobstetrical causes, and include only the former in computing the maternal mortality. An extreme of this policy is found in the recent Michigan study on maternal mortality[24] where fatalities from heart disease were classified among the nonobstetrical deaths. For this and other causes, approximately one-third of the total obstetrical deaths were regarded as nonmaternal or nonobstetrical. Granted that in many instances the cause of death is nonobstetrical, the presence of pregnancy may mask the condition, influence the clinical course, and alter the outcome ultimately. Unless one includes all deaths as defined above, the maternal mortality will become artificial and arbitrary. The following case has been chosen to illustrate that the failure to make a correct diagnosis and to institute treatment early were due to the fact that the symptoms were erroneously attributed to a term pregnancy.

CASE 2.—A 23-year-old primipara entered the hospital at 36 weeks of pregnancy, complaining of backache and intermittent abdominal pain. She was discharged 24 hours later with a diagnosis of false labor. She remained at home for three days and, according to the general practitioner, she was free of symptoms during this time. The patient re-entered the hospital in active labor and was delivered three hours after admission. She vomited several times after entering the hospital, but this was attributed to the effects of labor.

The baby was slow to breathe, despite the fact that the mother had little medication or anesthesia. Five minutes after delivery, during which time the physician was attempting to resuscitate the baby, the patient was noted to be in shock with a blood pressure of 80/40 and a pulse of 140. The blood pressure had been recorded as normal on admission, and presumably there was no evidence of shock prior to delivery. Vaginal bleeding was average and the placenta was delivered without undue blood loss. The patient was treated for shock. A medical consultant thought the patient's abdomen was slightly distended. During his examination, the patient vomited what was described as "coffee ground material." The medical consultant made a diagnosis of ruptured viscus, possibly due to an ulcer for which the patient had a positive past history. The obstetrical consultant favored a diagnosis of ruptured uterus, but vaginal palpation revealed it to be intact.

During the next forty-eight hours the patient received eight transfusions of reputed compatible blood. Supportive treatment consisted of Levophed, cortisone, antibiotics, parenteral fluids containing potassium, and gastric suction. Fever appeared, the pain continued, oliguria developed, and the patient became jaundiced. A mass was definitely outlined which was thought to be contained within the right broad ligament. The patient died in acute respiratory distress on the fifth postpartum day. The autopsy disclosed that the patient did not have a ruptured uterus, but a ruptured viscus which would have been manageable had the diagnosis been made prior to or immediately after delivery. While it might be argued that the diagnosis should have been made on the first hospital visit or immediately on the second admission, it is understandable why the condition was not recognized. Furthermore, if the patient had not been pregnant, surgical intervention undoubtedly would have occurred soon after the onset of symptoms.

In the Massachusetts series, where all maternal deaths are included in obstetrical causes, deaths from shock comprise about 25 per cent of the total number of deaths, in contrast to Michigan where the percentage of deaths from

this cause was approximately one-third of the total number of obstetrical deaths. When account is taken of the difference in computing the maternal mortality, and if based on the total deliveries, the percentage number of deaths from shock is nearly identical in the various series reported. It is evident that from state to state the problem of shock in obstetrics is of the same order of magnitude.

In deaths from shock due to injury and blood loss, *uterine atony* accounted for 41 deaths, or nearly half of the total. In an undetermined number of cases, however, atony was a late manifestation in the clinical course of the patient, and undoubtedly was due to shock brought on by blood loss from lacerations of the cervix and vagina. There is a clinical impression that the uterus tends to relax and not maintain its tone secondary to shock derived from causes other than atony. As commented upon in other maternal mortality studies, it is difficult to categorize deaths from trauma and atony, for in many instances there is an element of both.

There were 8 deaths which could be attributed directly to *trauma* of the birth canal; and while there were additional cases of rupture of the uterus they were in association with complications other than labor and delivery. As previously stated, there were many cases where trauma contributed to deaths assigned to uterine atony. Four of the deaths followed forceps procedures ineptly performed for disputable indications. One death from rupture of the uterus occurred from excessive suprafundic pressure in an attempt to deliver an infant with shoulder dystocia. One uterus ruptured from spontaneous tumultuous labor, while 2 cases of uterine rupture followed internal podalic version performed as the preferred method of delivery.

There were 5 deaths from *ectopic pregnancy,* and with one exception these patients entered the hospital moribund. *Premature separation of the placenta and placenta previa* accounted for 8 cases. An upset in the coagulation mechanism was thought to be present in some of these cases, and it appeared to be a contributing factor in a few deaths attributed to uterine atony. The diagnosis was not made, however, unless it could be definitely proved. There were 3 deaths classified as cases of acquired *hemophilia.* Comparatively speaking, there was a rather large percentage of deaths from *inversion of the uterus,* for there were 6 in this series. There were 2 patients who lost their lives from a retained placenta associated with *placenta accreta.*

There were a number of deaths from *sepsis,* and of these shock was a clinical feature in 7 cases. There were 5 cases of septic abortion; the remaining 2 had peritonitis in nonobstetrical surgical conditions. There was one patient who died of shock from *myocardial infarction.* This individual was known to have severe hypertensive disease prior to pregnancy. There were only 2 deaths which could be attributed to *miscellaneous* causes where shock appeared. One patient had a pheochromocytoma, found at autopsy; the other patient had toxemia with an element of electrolyte depletion in association with prolonged treatment with Diamox.

Embolism of the pulmonary system has not been included in deaths due to shock for reasons already mentioned. The only exception is the case cited of *amniotic fluid embolism* where the patient died in shock associated with severe hemorrhage. Accordingly, this case is classified in the category of shock due to blood loss. It is of passing interest that there were 7 deaths from amniotic fluid embolism in this series. Death was assigned to this condition only where autopsy findings verified the diagnosis. In addition, there were 9 deaths from pulmonary embolism, proved by autopsy.

The sequelae of shock are amplified by a series of patients with acute renal failure observed during a comparable seven-year period, at the Peter

Bent Brigham Hospital. A Kolff-Merrill artificial kidney, under the supervision of Dr. John Merrill, provided the incentive for physicians in New England and elsewhere to refer patients with renal complications of pregnancy to this institution. These cases, 47 in number, are tabulated according to their etiology and eventual outcome in Table I.

TABLE I. CAUSATIVE FACTORS IN ACUTE RENAL FAILURE IN PREGNANCY (47 CASES)

	NO. OF CASES		TRANSFUSION REACTION	DEATHS
I. Premature Separation of the Placenta				
a. With toxemia	5		1	1
b. Without toxemia + cesarean section	6		1	2
		11		
II. Abortion				
a. With a hemolytic reaction	2		-	-
b. With a transfusion reaction	2		2	-
c. Shock + sepsis	2		-	1
		6		
III. Postpartum Hemorrhage				
a. Uterine atony	2		1	-
b. Repeat section + shock	3		1	-
c. Traumatic pelvic delivery + toxemia	3		-	1
d. Uterine atony + toxemia	4		-	2
e. Amniotic fluid embolism	1		-	-
f. Hydatidiform mole	2		-	-
		15		
IV. Transfusion Reaction				
a. Prepartum anemia	1		1	-
b. Postpartum anemia	1		1	1
c. Prophylactic transfusion + cesarean section	2		2	-
		4		
V. Toxemia				
a. Persistent postpartum oliguric phase		3	-	-
VI. Placenta Previa				
a. Pelvic delivery + atony	1		1	-
b. Cesarean section + atony	3		2	1
		4		
VII. Periarteritis Nodosa		2	-	2
VIII. *B. welchii* Infection		1	-	1
IX. Diabetic Ketosis		1	-	1
		47	13	13

Comment

Pertinent to this discussion is a consideration of the obstetric factors which contribute to the causation of shock, and the complications, techniques, and procedures which may influence the ultimate outcome.

Shock From Injury and Blood Loss.—As in other surveys, injury and blood loss accounted for nearly all of the deaths from shock.

Atony: In this series uterine atony was the chief cause of death. The profession is quite aware that atony is more likely to develop in conditions which interfere with normal uterine contractility. Whatever controversy there is, therefore, concerns the definitive rather than the preventive treatment of uterine atony, particularly the value of uterine

tamponade. Many clinicians, perhaps the majority, favor bimanual compression of the uterus in the treatment of bleeding from atony, and argue that if the uterus does not respond to oxytocic drugs the insertion of a gauze pack will be of little benefit. They oppose this procedure, believing that the uterine pack prevents the organ from contracting to its immediate, normal postpartum size. Hence, the endomyometrial blood vessels may remain patent, allowing uterine bleeding to continue.

Postpartum hemostasis, however, is not completely attained simply by constriction of the endomyometrial blood vessels. Thrombosis of the decidual vessels is necessary for the control of bleeding of the uteroplacental site.[31] Evidence that these vessels must become thrombosed for complete hemostasis is derived from the clinical behavior of postpartum patients who have received excessive amounts of heparin or Dicumarol, or who have developed hypofibrinogenemia. Uncontrolled bleeding has been observed in these individuals in the absence of uterine atony. Similar to the effect of a pressure pack to control oozing from body surfaces elsewhere, it is inferred that the irritation of a gauze pack will promote thrombosis of the vessels of the uteroplacental site. Moreover, the presence of a foreign body, in this instance a gauze pack, will encourage the uterus to contract and collapse the endomyometrial vessels.

As the maternal deaths in this series are reviewed, however, it is difficult to establish the fact that the uterine pack has therapeutic value. The excuse may be offered that in these cases the uterus was improperly packed or was packed as a last-resort procedure. By contrast, in a total of over 16,000 deliveries on the house service at the Boston Lying-in Hospital over this seven-year period, the diagnosis of postpartum hemorrhage was made in 270 instances, or 1.7 per cent. During this period the uterus was packed 30 times, and no patient was subjected to hysterectomy for uterine atony. On the private service in the same period of time there were some 24,000 deliveries, and the uterus was packed in 46 cases. Hysterectomy was performed in one instance when bleeding occurred two weeks post partum, after curettage and packing failed to control bleeding from subinvolution of the placental site. The other instance was in a patient in whom bleeding, presumably from atony, began three hours after delivery in a labor conducted according to the tenets of so-called "natural childbirth."

Thus, in a total of more than 40,000 deliveries there were 2 hysterectomies for uterine atony and one death from obstetrical hemorrhage in the hospital during this seven-year period. The latter patient was an unregistered grand multipara who entered the hospital exsanguinated and in irreversible shock, the result of spontaneous rupture of the uterus from dystocia due to an excessively large infant.

While the uterus was packed infrequently in the treatment of atony, and less frequently since the use of intravenous Pitocin drip medication, it is still the policy at the Boston Lying-in Hospital to use a uterine pack on occasion. To do otherwise seems unrealistic for a variety of reasons. Where the physician is the only available medical person to contend with the hemorrhage and to institute blood replacement, the method of uterine compression seems somewhat impractical. Moreover, this method of treatment of uterine atony is predicated on the concept of a single source of bleeding. Certainly in cases of prolonged labor and difficult forceps operations, uterine atony and lacerations of the birth canal are sometimes associated. Consequently, with a dual origin for the bleeding, it seems obvious that the uterus should be packed forthwith and the lacerations quickly closed with appropriate sutures. To ignore the value of uterine pack, moreover, means that patients in whom atony cannot be controlled by uterine compression, and after a limited trial of oxytocic therapy, must be subjected to immediate supracervical hysterectomy. Uterine packing may alleviate the necessity for this operation, and where medical personnel is limited it may allow the surgeon time to prepare the patient for hysterectomy by first restoring the blood loss.

To avoid defeating the therapeutic value of uterine tamponade, however, excessive amounts of gauze must be avoided. The space occupied by two gauze strips, each measuring 1½ inches wide and 3 yards in length, will not exceed the immediate postdelivery volume of

the cavity of the well-contracted uterus as determined objectively at the time of cesarean section. Consequently, if the amount of gauze is restricted to this amount there is no reason to suspect that the uterus will be distended abnormally by the presence of the pack.

Preferably the uterus is packed manually rather than by using a mechanical packer. While there are certain advantages to the use of this instrument, there is also the danger of incorrect packing. Introducing an instrument into an extremely atonic uterus is not without hazard, while failure to place the end of the packer at the top of the fundus will result in faulty packing. It is readily admitted that the therapeutic value of the procedure is lost if the uterus is packed incorrectly. In order to avoid this possibility, the gauze strip is introduced into the uterus by the vaginal hand and beginning at the fundus the uterus is carefully packed from the top downward. Repacking is not recommended in the event that bleeding should continue or recur after removal of the pack. There is no reason to suspect that repacking will be more effective provided the procedure has been correctly performed initially, while the delay may result in further blood loss. Should bleeding recur, supracervical hysterectomy should be strongly considered and the operation should not be postponed until the patient has again entered into a state of shock.

Forceps procedures and internal podalic version: Trauma deaths in this series followed ill-advised forceps procedures and internal podalic version. While skill, experience, and judgment are factors which influence immeasurably the frequency of trauma to the birth canal, adherence to proper techniques of normal as well as forceps delivery may obviate this complication with its possible blood loss and gynecologic sequelae.

In the human female, birth is seemingly more difficult than in other primates, at least as it may be influenced by the shape and contour of the pelvis. In the subhuman primates, the pubic arch flares widely and, consequently, with birth the perineum is permitted to dilate uniformly. The sacrum, moreover, ends at the inlet so that whatever bony obstruction occurs is restricted to the superior strait. It is of passing interest that despite these apparent advantages in the lower primate the fetal vertex is born in an extreme degree of flexion and in a position of occiput posterior. By contrast, the human female must deliver a fetus with a comparatively larger vertex through an outlet which is confined by a pubic arch that permits only the posterior component of the perineum to dilate. The latter in turn must either stretch enormously or be lacerated. Accordingly, this might be regarded as the "natural" way.

A number of notable contributions have been made in the technique of delivery to modify this natural method of delivery and to protect against the damaging effects of birth on the fetus and soft parts of the mother. While no lengthy discussion is proper here, it might be asked whether certain of the techniques of delivery, some devised specifically to prevent trauma, long recommended and generally accepted and taught, are necessarily correct. For example, does the exaggerated lithotomy position widen the bony outlet and thereby aid in the birth at the inferior pelvic plane? If so, it is obvious that this position also causes tension on the perineum and the surrounding soft tissues of the lower vagina. This suggests that these structures are better protected if the patient's thighs can be lowered, preferably by human leg holders, at the time that the presenting part is being born. This provision for lowering the patient's thighs also diminishes significantly any tendency to extension of the episiotomy incision.

It is generally accepted that the so-called Ritgen's maneuver is a necessary procedure in delivery of the presenting part. It is commonly stated, moreover, that in order to present the smallest diameter of the fetal head to the outlet some degree of extension of the head is required. Actually, the maneuver presents the larger occipitofrontal diameter to the outlet. Both the procedure and the reasons given for its use are open to question.

Like others before him, Ritgen[34] observed that the occiput rotated, as he described it, about the inferior border of the symphysis. He was cognizant of the severe lacerations which invariably occur when the presenting part is born during the expulsive efforts of the mother. To try and avoid these lacerations, Ritgen recommended that the presenting

part be delivered over the perineum between contractions according to his familiar technique. In a period before asepsis and of little anesthesia, Ritgen's maneuver was a distinct advance in preventing trauma to the birth canal at the time of delivery. Ritgen[34] must have realized, however, that lacerations were common despite this procedure, for in a percentage of his cases he resorted to what he called scarification, making seven or eight incisions about the introitus, presumably to promote dilatation.

In practice, Ritgen's maneuver, despite an episiotomy, frequently causes laceration about the urethra and clitoris and disruption of the endopelvic fascia, through accentuating the pressure of the rotating occiput against these structures. It is suggested, therefore, that the vertex be maintained in complete flexion until the occiput has passed the inferior border of the symphysis. Accordingly, the smaller suboccipitobregmatic diameter of the vertex passes through the outlet rather than the larger occipitofrontal diameter. This same principle applies to forceps delivery, for nothing is more damaging to the soft tissues of the vagina than extending the fetal vertex till the forceps handles overlie the patient's pubes. This attempt to mimic the Ritgen maneuver tends to cause lacerations in the lateral sulci and anterior vaginal wall, areas which are noted for their vascularity.

While routine episiotomy has become an accepted procedure, it is suggested that it be performed when the vertex becomes barely visible. In the more difficult forceps operations, if the incision is made at this early time it will tend to prevent lacerations from occurring elsewhere in the lower vaigna. It is believed that adherence to the ideas here expressed will not only decrease maternal soft-tissue damage at the time of delivery, but will eliminate in large measure the need for any subsequent plastic or other gynecological procedures in later life.

Except in outlet forceps operations, these objectives are difficult to achieve without the use of axis traction. To try and guide the vertex downward through the mid-axis of the pelvis, using the Simpson or some comparable type of forceps and applying traction posteriorly and downward (Saxtorph-Pajot maneuver), is fraught with grave danger of trauma to the maternal soft parts and damage to the infant. It is recommended that this outmoded and obsolete maneuver be placed in the same category as the high forceps operation, neither of which has a place in modern obstetrics.

The more difficult obstetrical procedures of midforceps and internal podalic version with their hazard of trauma are performed less frequently than formerly and rightly so. This is acceptable only by making cesarean section a safer procedure through better anesthesia, the control of infection by antibiotics and chemotherapeutic agents, and the reintroduction with refinements in the technique of the extraperitoneal type of cesarean section. Toward this end, more important has been the development of accurate methods of x-ray pelvimetry by Caldwell, Moloy, and D'Esopo and by Thoms, and their classical studies of the architecture of the female pelvis. From these observations the internal examination of the obstetrical pelvis becomes more meaningful, for it emphasizes to the physician those anatomical variations which can impede labor and possibly cause trauma at the time of delivery. While readily demonstrable on x-ray pelvimetry, these important anatomical landmarks can be identified on pelvic examination by any competent and willing clinician.

Useful as x-ray pelvimetry is both as a clinical and teaching aid, I believe that if traumatic pelvic delivery is to be avoided the safest method of delivery must on occasion be decided by the findings at pelvic examination during the second stage of labor and with the patient anesthetized. These are the few patients with borderline pelves, in whom pelvic delivery is anticipated but who fail to make satisfactory progress in the latter hours of a trial labor. In the most troublesome cases the choice of the method of delivery is between a possible midforceps operation, usually in the presence of borderline midpelvic and outlet contracture, or the alternate procedure of cesarean section on the patient who in most instances has experienced prolonged labor and is potentially infected. The question to be decided is, what is the safest procedure for the mother and her infant? Careful assessment

of the midpelvis and outlet and an estimation of the size of the fetal vertex by pelvic examination under the conditions referred to will afford the experienced clinician sufficient information for him to choose the correct procedure. Ideally, the examination should be conducted in the operating room where preparations have been made for either pelvic or abdominal delivery and the method of anesthesia planned accordingly.

Cesarean section: It is difficult, if not impossible, on the basis of present-day reports to determine whether in these cases extraperitoneal cesarean section or lower segment transperitoneal cesarean section combined with antibiotic therapy has a lower mortality rate in the potential or frankly infected case.[10, 12, 20, 48, 49] A comparison of the results of some of the larger maternity services indicates that in those institutions where extraperitoneal cesarean section is employed the incidence of cesarean section following a trial labor tends to be lower than where the lower segment transperitoneal operation is used. It is recognized that this is subject to a number of variables, including the frequency of abnormal pelves which may vary from one group of patients to another. The results suggest that in hospitals where the transperitoneal cesarean section is advocated the operation is performed earlier in a test of labor because of the threat of intraperitoneal infection. In other words the primary cesarean section incidence for unproductive labor, regardless of cause, is slightly higher where the latter is employed in comparison to our experience where extraperitoneal cesarean section is utilized.[10, 12] This suggests that recognition is being given to the hazard of peritoneal infection in cases of prolonged labor, a factor which need not be considered where the extraperitoneal type of cesarean section is employed. Further, there is no comparable group of patients delivered by transperitoneal cesarean section and antibiotics to those grossly infected cases reported by McCall[22] who were safely delivered by extraperitoneal cesarean section.

The technique of extraperitoneal cesarean section (Waters type) not being difficult, it appears logical to avoid peritoneal contamination by the use of this operation or the Smith exclusion procedure and at the same time take advantage of the value of antiobiotics and chemotherapeutic agents which the advocates of transperitoneal cesarean section believe are sufficient in the potentially infected patient.[48, 49] Unfortunately, *there is no sure way of excluding the presence of intrauterine infection before operation.* In the event that the decision is to perform an abdominal delivery in preference to a difficult forceps extraction in prolonged labor cases, the extraperitoneal type of cesarean section is the procedure of choice at the Boston Lying-in Hospital.

Placenta previa: While no patient in this series apparently lost her life from bleeding during the last trimester of pregnancy prior to delivery, the number of deaths listed under the category of prepartum bleeding in other series re-emphasizes the dangers inherent in this complication. A disturbing feature of one study was the fact that 48 cases, or 16 per cent of the total deaths, were due to antepartum bleeding.[27] Undoubtedly some deaths in patients who had bled during the last trimester occurred prior to delivery and others as a consequence of delivery. Actually, there were a number of the latter in the series being reported and, in this supposedly enlightened age, two followed internal podalic version with placenta previa in the presence of viable infants. There were several deaths from abruptio placentae also, in which the patients were ill prepared for delivery through lack of blood replacement, and in some of these a coagulation defect was obvious. In reality, these patients lost their lives because of pre-delivery blood loss, and their deaths should be classified as due to prepartum bleeding.

In some respects, the management of patients who bleed in the last trimester of pregnancy is more difficult today. The patient is anxious to avoid prolonged costly hospitalization if possible, while the physician must be mindful of what is best for the patient. Actually, the majority of patients who experience an episode of bleeding in late pregnancy will fail to demonstrate any cause for the bleeding. Some 5 to 6 per cent of patients bleed in the last trimester, but only one out of 3 will prove to have placenta previa or will develop premature separation of the placenta of a degree that will demand further investigation and treatment. The problem, therefore, is to screen and carefully treat the patients who will prove to have placenta previa. The practical question must be answered whether patients

who experience vaginal bleeding in the last trimester of pregnancy are to be hospitalized in every instance. In other words, at what time in pregnancy and under what circumstances is the life of the patient with placenta previa seriously threatened?

In recent years there has been a tendency to treat patients suspected of having placenta previa expectantly, at least prior to the last month of pregnancy. The objective of this policy is laudable, for it hopes to postpone definitive obstetrical interference until the fetus attains a state of maturity which will insure its survival. Where expectant treatment of placenta previa is practiced, the question which demands an answer is to what extent is the mother or fetus endangered by episodes of recurrent bleeding? The opinion has been expressed that blood loss from recurrent hemorrhage from placenta previa never reaches serious proportions unless the bleeding is precipitated by vaginal examination or manipulation. While no patient lost her life from placenta previa prior to delivery in this series, it is perhaps well to restate that other studies of maternal mortality indicate that some patients died with a history of recurrent episodes of bleeding.[27] I had the unhappy experience of participating in the care of a patient with placenta previa who died from recurrent exsanguinating hemorrhage with irreversible shock when about to enter the operating room for definitive diagnosis and treatment. This occurred despite a cesarean section performed within 20 minutes after the onset of *spontaneous* bleeding and with ample amounts of blood replacement. Other cases have been observed where the patient would have undoubtedly lost her life had it not been for the fact that she was in the hospital under observation and was delivered immediately by cesarean section, receiving prompt and adequate blood transfusions. In fairness to the problem, however, these patients were within a month of term, and all had either a complete or partial placenta previa, something which cannot be foretold with certainty until the patient is examined vaginally.

From the literature, it is difficult to document whether any patient with placenta previa has bled to death from an initial hemorrhage prior to the thirty-fourth or thirty-fifth week of pregnancy. Consequently, in recent years the Boston Lying-in Hospital has adopted the policy of not hospitalizing patients with bleeding in late pregnancy occurring prior to the thirty-second week, provided the bleeding is minimal and the physical examination shows the uterus to be soft, nontender, and without spasm, and the fetal heart tones to be normal. The patient is instructed to remain at bed rest and to report recurrent bleeding immediately and is warned of the dangers of sexual intercourse. The patient is seen at frequent intervals thereafter, and between the thirty-second and thirty-fourth weeks of pregnancy an attempt is made to localize the placenta radiographically. Placentography performed before the thirty-fourth week of pregnancy is generally unsatisfactory. In the event that x-ray examination proves positive for placenta previa, the patient must enter the hospital for observation and further study. On the other hand, if the placenta is clearly located in the upper segment of the uterus, the patient may return home and resume her normal activity. In the interim, should bleeding recur or the patient's history show more than a single episode of bleeding when she was first seen, it is mandatory that she enter the hospital immediately. It is contemplated that this policy saves days of needless hospitalization without exposing the patient to any undue risk from recurrent hemorrhage. Except for an extremely *gentle* speculum examination to exclude cervical pathology, these patients are never examined either rectally or vaginally except in the operating room with every provision made to treat the patient forthwith should the diagnosis of placenta previa be verified.

While conservative or expectant treatment is the preferred method of management until the last month of pregnancy in patients suspected of placenta previa, the mother's welfare must never be jeopardized in a desperate and sometimes futile effort to salvage an immature infant. Even Macafee[21] and others who have been strong advocates of the expectant treatment of placenta previa find no medical advantage to extending this form of treatment beyond the thirty-fifth week of pregnancy.

Placenta accreta: The problem of retained placenta affords a situation which serves to illustrate what is meant by providing maximum safeguards for the patient. Apparently,

some clinicians regard manual removal of the placenta as a harmless procedure, but we feel that retention of the placenta is a major complication of delivery, whose risk has been but partially removed through the chemotherapeutic control of infection.

Obviously, in the presence of an alarming hemorrhage from partial separation of the placenta during the third stage of labor manual removal must be performed immediately. Where the placenta fails to separate spontaneously or be expelled and the degree of bleeding is such that the patient is not in immediate danger from hemorrhage, one should consider a more deliberate policy of safe management. In a recent series of cases of manual removal at the Boston Lying-in Hospital,[1] some degree of placenta accreta occurred in approximately 10 per cent of the cases. During the seven-year period, from 1949 to 1955, inclusive, on the house service there were 13 cases of placenta accreta, 4 of which occurred in uteri with a previous cesarean section scar and 3 were in association with placenta previa. Of the remaining 6 cases, all of the focal type, 3 required eventual hysterectomy for the control of hemorrhage, and 3 were managed by curettage and uterine pack. While total placenta accreta is an extremely rare entity, lesser types involving one or more cotyledons are not infrequent although they often are not recognized as such or so reported. In the 2 maternal deaths which occurred in the maternal mortality series, both mothers were lost because of the inability of the physician to recognize and treat the condition. One patient died from hemorrhage several hours after delivery by cesarean section. There was apparently an unrelenting reluctance on the part of the operator to consider hysterectomy in the face of an obvious diagnosis of placenta accreta.

Due to the relative frequency of placenta accreta, a planned procedure is recommended, namely, to remove the placenta manually in the operating room under the so-called double set-up procedure within the hour following delivery. This policy demands that preparations be made for laparotomy, in spite of the fact that the latter will rarely be resorted to. This specific preparation is often regarded with considerable skepticism, and hindsight in most instances would allow one to dispense with these tedious details. It is more than justified, however, when the rare case is encountered where the control of hemorrhage is dependent on immediate hysterectomy. This and many other obstetrical situations might be cited in which this philosophy of "being able to get away with it" can on occasion end in disaster. In other words, there are no shortcuts to safe obstetrics.

Inversion of the uterus: While inversion of the uterus is commonly attributed to an improper conduct of the third stage of labor, frequently there is no obvious cause. Failure to appreciate this fact may lead to a false sense of security with a delay in diagnosis, particularly when the placental stage has been normal. Although inversion may occur some time after delivery, undoubtedly in the majority of instances it develops simultaneously with the separation and delivery of the placenta. The mortality appears in cases where the condition is not recognized until several hours after delivery.[3, 8]

As emphasized by Kellogg, Bell, and others, the method of treatment is determined by the duration of the time interval after delivery when the inversion is recognized. If identified at delivery, immediate replacement is simple and easy and the patient usually recovers from her shock promptly. If recognized any time later, the cervical ring is already producing constrictive passive congestion causing the corpus to enlarge rapidly, on occasion to the size of a large grapefruit. Any attempt at vaginal replacement is fraught with grave danger for the chance of success is poor and further manipulation will accentuate the bleeding and cause irreversible shock. By preference, after a period of time devoted to energetic treatment of the shock, a less traumatic procedure is believed to be the abdominal approach, utilizing the operation of Huntington or Haultain to reduce the inversion. Replacement of the corpus by this means is quickly accomplished with a minimum of shock.

Amniotic fluid embolism: This was observed with somewhat more frequency than was anticipated in this series, for the frequency was akin to that observed in massive pulmonary embolism. Whether this complication was a contributing factor in other deaths from hemorrhage

in this series is impossible to determine with any degree of accuracy. It can now be accepted that the sudden appearance of severe respiratory distress during an otherwise normal labor or delivery is pathognomonic of this syndrome. The factor which seems to be of etiological importance in the development of this condition is a rapid and tumultuous labor which may on occasion be associated with the overenthusiastic use of pituitary preparations. In any event, should the patient survive the initial embolic insult, hemorrhagic manifestations are likely to develop and, in addition to resultant uterine hemorrhage which may be wrongly attributed to atony, there may be generalized bleeding from mucous membranes indicative of a clotting defect. The diagnosis should be considered when bleeding continues after all causes for postpartum hemorrhage have been excluded.

Ectopic pregnancy: The prevention of deaths from extrauterine pregnancy is dependent primarily on early diagnosis and treatment. An unpleasant feature of the deaths in this series was the failure of the patients to seek medical care prior to fatal rupture, dying at home or entering the hospital moribund. These castastrophes will continue until womankind realizes the importance of early prenatal care which, as the profession well knows, should begin within two weeks after the missed period.

The recognition of a ruptured tubal pregnancy is obvious, but the diagnosis of ectopic pregnancy is notoriously uncertain prior to rupture. In view of the fact that some 20 to 25 per cent of women experience minor degrees of vaginal bleeding during the first trimester of pregnancy, the diagnosis must be considered constantly.[40] *Good medical care dictates that no patient under prenatal supervision should ever have a tubal pregnancy reach the stage of rupture.* To avoid this possiblity, however, the history of vaginal staining must never be taken casually. These patients must be seen frequently, and one must not be reluctant to perform a vaginal examination biweekly if necessary until convinced either that the pregnancy is normal or that the patient should be hospitalized for further investigation.

Shock From Sepsis.—The role of sepsis must be reckoned with both as a primary cause of shock and as a contributing factor in shock due to injury and blood loss. The recently reported observations of Studdiford and Douglas[42] emphasize the interrelationship between bacteremia and shock in the obstetrical patient and the clinical problems involved. Where sepsis is accompanied by shock, hemolysis, acute renal failure from either tubular necrosis or possibly from bilateral cortical uecrosis, and adrenal insufficiency are further complications. When associated with bacteremia, there may be near complete destruction of the adrenal (Waterhouse-Friderichsen syndrome).

Myocardial Infarction.—This is rare in women of the childbearing age. Shock from this cause in pregnancy would indeed be unusual, for only some 15 per cent of patients with myocardial accidents develop shock. It is of interest, however, that the one patient who died of coronary artery disease in this series presented the characteristic clinical picture of shock.

The Sequelae of Shock

While the entire organism is under insult in shock, in pregnancy the adenohypophysis and renal parenchyma appear particularly vulnerable. In classical contributions Sheehan[39] has demonstrated that obstetrical shock is the chief cause of a panhypopituitarism. Suffice it to say, necrosis of the adenohypophysis was found in some of these patients, as well as in individuals who died from anuria. Because of its enlargement in pregnancy and portal-like system of blood supply, Sheehan has proposed an acceptable explanation as to why shock in the obstetrical patient may cause necrosis of the anterior lobe of the pituitary, a complication not seen in a nonpregnant individual with shock.

Shock is the common denominator in the causation of acute renal failure. To what extent shock in obstetrics contributes to the etiology of acute renal failure is perhaps not generally appreciated. In reality, some 20 to 40 per cent

of the cases of acute renal failure are associated with complications of pregnancy. Stating it another way, of female patients with acute renal failure, approximately 50 per cent are or have been recently pregnant. The anuria in most instances is due to acute tubular necrosis, although in the absence of renal biopsy bilateral cortical necrosis cannot be excluded.[28]

Intravascular hemolysis due to a transfusion of incompatible blood was an important cause of acute renal failure in the 47 cases here reported. Such errors occur when emergencies arise and personnel are under pressure. They are always preventable in retrospect, but the inherent dangers of blood transfusion are hardly an excuse to withhold blood. Rather, the challenge is to maintain a blood bank which does not make mistakes. By contrast, therefore, many of the patients developed acute anuria because of inadequate blood replacement, and in a few cases hemorrhagic shock was the direct sequel of an ill-advised traumatic obstetrical maneuver. Although in many of these patients toxemia was a prominent feature, often sufficiently severe to serve as the indication for obstetrical intervention, the renal failure was the result of shock during and after delivery. The presence or absence of shock must be taken into account when the etiology of any apparent residual renal damage in the toxemic patient is assessed.[28]

Treatment

During the discussion reference was made to various conditions which bear on the causation of shock and the obstetrical ways and means to avoid it. The following remarks will consider some of the aspects concerned directly with the treatment of shock itself.

The definitive treatment of shock begins with the recognition and correction of iron deficiency and other forms of anemia, for certainly patients who enter labor with less than 10 Gm. of hemoglobin are not suitably prepared for an anesthetic, are less resistant to infection, and are extremely vulnerable to the ravages of shock should it arise. When time permits, medical correction of the anemia is preferred, either in the form of suitable preparations of iron, or folic acid in the case of megaloblastic anemia. While clinicians in the past have expressed the opinion that transfusions given during pregnancy may affect the fetus adversely, in retrospect these could have been cases of Rh sensitization, a factor not then discovered. Whenever necessary, therefore, prelabor transfusions should be given to remedy a significant deficiency in hemoglobin concentration.

Essentially the treatment of shock is the restoration of effective blood volume and, except for shock due to sepsis and myocardial infarction, requires rapid and efficient blood replacement in amounts equal to the blood loss. In sepsis, however, blood transfusion often fails to correct the shock until the infection is brought under control. The dangers of overtransfusion in the obstetrical patient are negligible unless shock reaches an irreversible state where signs of congestive heart failure can appear. There is no convincing evidence that arterial blood replacement is more effective than the venous route in the normal heart where the cardiac output responds to an increase in venous filling.[16] Intra-arterial transfusion is of special benefit only where there is need to raise the aortic pressure and force blood through the coronary vessels, as in the case of myocardial infarction or in cardiac arrest.

The arterial pressure can be raised by pressor drugs,[6] but these are not without danger, while their effects are transient. Furthermore, these drugs may mask blood volume deficiency, and what perhaps is more significant is the fact that their therapeutic effect is at the expense of an increase in renal vasoconstriction. Undoubtedly vasopressor drugs find their greatest usefulness

in patients with shock due to sepsis where the total blood volume may on occasion be normal. In cases of severe bacteremia, norepinephrine will raise the blood pressure when it has failed to respond to blood transfusion.[42] It is generally accepted that plasma and plasma expanders are not substitutes for whole blood. Furthermore, expander substances have no therapeutic advantage over plasma, while complications affecting the clotting mechanism have been reported following their use.[18]

When damage to the anterior lobe of the hypophysis or adrenal is suspected, ACTH and adrenocortical therapy may influence the outcome. This applies especially to cases where shock is prolonged, anuria develops, and sepsis is severe.[14]

It has long been known that electrolyte depletion will result in shock, and clinical experience attests the fact that it is difficult to maintain the blood pressure in a patient with a salt depletion syndrome.[26, 35] In an effort to control fluid retention as a part of prenatal care, sodium restriction may exceed the physiologic need. Tatum[44] has recently reported that in toxemia the serum sodium levels may occasionally be considerably lower (±125 meq. per liter) than in normal pregnant women. The dangers of prolonged restriction of sodium and of diuretics whose physiologic action depends upon the creation of acidosis must be recognized. As suggested by Tatum, the administration of sodium, and in some instances potassium, may be sound therapy in a patient who develops shock, especially if the hypotension seems out of proportion to the blood loss. Electrolyte depletion in the pregnant woman, however, must be extremely rare, and the advisability of the administration of additional sodium must be viewed with caution. Furthermore, in the toxemic patient with low serum sodium, personal experience indicates that the depressed serum sodium level may fail to change following sodium chloride therapy.

In recent years it has become evident that under certain obstetrical circumstances an upset in the blood clotting mechanism may occur, contributing significantly to the degree of blood loss and shock.[31] This phenomenon has been observed in long-standing death of the fetus in utero, the severe form of abruptio placentae, and as a secondary effect of amniotic fluid embolism.[31, 32] On the basis of present evidence the clotting defect appears to be due mainly to a reduction in the plasma fibrinogen concentration. While other factors of blood clotting may be decreased, especially platelets, Ac-globulin, and prothrombin activity, the reduction of these elements does not reach a hemorrhagic level. While no fibrinogen may be detected on occasion in the maternal blood in these cases, in the majority of instances it is somewhat less than 100 mg. per 100 ml. of blood. A fibrinogen concentration below 150 mg. per 100 ml. in the pregnant patient is now generally regarded as abnormal.

A defect in clotting has been noted following incompatible blood transfusion. Undoubtedly a hemorrhagic diathesis was a factor in the shock of these patients who developed anuria following the administration of mismatched blood. Several components of clotting are deranged and a heparinoid anticoagulant has been identified.[23] In addition to fibrinogen therapy, toluidine blue or protamine sulfate has been suggested to counteract the anticoagulant effect.

In contradistinction to the syndrome of hypofibrinogenemia, several reports have appeared in the literature indicating that an acquired hemorrhagic diathesis resembling hemophilia may develop and be recognized late in pregnancy or a few weeks to several months after delivery.[5, 13, 15, 29] The clotting time of normal blood is definitely prolonged upon the addition of the patient's blood, suggesting that the coagulation defect is the result of a circulating anticoagulant. The latter is believed to interfere with antihemophiliac globulin

or the precursor of thromboplastin and, consequently, has been referred to as an antithromboplastin. In this series of fatal cases there were two individuals who developed such a coagulation defect (acquired hemophilia). In the present state of knowledge the prognosis must be guarded in these patients, for the only known treatment consists of multiple transfusions in contrast to that of hypofibrinogenemia where the administration of Cohn's Fraction I is capable of remedying the coagulation defect.

Despite the fact that important advances have been made in methods of processing blood, the immediate administration of sufficient amounts of blood continues to remain the major problem in the definitive treatment of shock.[46, 47] The problem is reduced to the question how best to provide this lifesaving service.

As stated by Crosby,[7] no woman should be permitted to die while her blood is being typed and cross-matched. While the safety of Group O blood of high and low titer and A and B isoagglutinins perhaps has not been definitely proved, certainly few incompatible reactions were encountered when the universal system was used during World War II and the Korean War. In fact, most of the reactions recorded in Korea were due to mismatching of type-specific blood procured locally.[7] The risk of inadequate group-specific typing must be calculated therefore and reckoned with, and certainly the chance of mistakes is enhanced when it is necessary to procure blood quickly. While it is true that approximately 35 per cent of group O donors have significant isoagglutinins, these plasmas rarely cause a reaction and this can be avoided by the addition of Witebsky's soluble blood-group-specific A and B substance.[7] In conditions which require transfusions to be administered periodically over a long span of time, unquestionably type-specific blood is advisable for it is known that the A and B isoagglutinins remain in the recipient for some two to three weeks after transfusion. Experience from the Blood Bank at the Boston Lying-in Hospital, however, using only type O positive and negative blood, indicates that this is not an objection in the management of patients with obstetrical hemorrhage.*

The use of "AB group-specific substances" in each unit of blood to neutralize the anti-A and anti-B titer of group O blood has proved entirely safe, since no patient, even those receiving multiple transfusions, and especially the few patients retransfused weeks or months later, showed any reaction. Finally, there was no evidence that the materials had been antigenic and had raised the anti-A and anti-B levels of the recipients to a degree where erythroblastosis due to the ABO complex could be induced in subsequent pregnancies of such women. These results indicate, therefore, that the use of only group O, Rh-positive and Rh-negative blood is justified.

Newly developed transfusion equipment obviates other sources of danger such as air embolism and bacterial contamination.[2, 46] The latter, while rare, is often fatal. Studies have shown that when blood was collected under vacuum in glass equipment the incidence of contamination was approximately 3 per cent, in contrast to situations when blood was collected into plastic

*During the past five years, through 1955, 1,120 patients have been given transfusions averaging 224 patients per year. Over 2,000 units of blood were given, and many of the patients had multiple transfusions, the largest number given to a single patient having been 26 units of blood. In addition, 60 units per year were used for exchange transfusion, making in all approximately 2,500 units used, without any deleterious reactions. Almost 25 per cent of the patients receiving blood transfusions required Rh-negative blood. In a few instances such blood was given to patients who had not been typed in advance because of the dire emergency requiring immediate transfusion, and then Rh-positive blood was used thereafter when typing showed the recipient to be Rh-positive. In most cases, however, the Rh-negative blood was given only to Rh-negative patients, which reflects a high percentage of Rh-negative women coming into the hospital for ordinary and special care because of the ability of the institution to manage and cope with difficult problems, particularly involving blood group incompatibility. (I am indebted to Dr. Louis K. Diamond, Director of the Blood Grouping Laboratory, for these data.)

equipment when the rate of contamination was reduced to 0.6 per cent.[2] The common criticism of failure to get blood into the recipient can be removed by sizable infusion needles (17 gauge) and proper filters to prevent fibrin clot in the recipient set.[46]

Finally, experience gained from this study and from those in other states discloses the startling fact that the majority of hospitals with obstetrical services do not have blood banks, nor do they utilize a blood repository. Apparently most hospitals still rely on donor lists to provide blood for transfusion purposes.

Summary

A review of maternal mortality in any area of the United States indicates that a significant number of patients continue to lose their lives from shock. These deaths are largely preventable through more careful obstetrics when performed in hospitals with the facilities to meet the emergency treatment of shock.

Except for the case of myocardial infarction and the occasional case of sepsis, the treatment of shock as herein defined depends on early administration of blood in amounts adequate to restore the effective blood volume. Lack of adequate blood replacement, if it does not result in death, may lead to severe renal and pituitary damage. It is apparent that shock in obstetrics cannot be treated effectively by blood obtained from a blood repository outside the hospital or from donor lists. It can be met only by the hospital's own blood bank and by the storage of suitable blood in adequate amounts on the delivery floor. It is suggested that no hospital be allowed to care for pregnant women if it is unable to meet this essential requirement.

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Discussion

DR. M. EDWARD DAVIS.—Shock and hemorrhage constitute the number one cause of maternal mortality in Illinois and in the nation as well as in Massachusetts. In an excellent study of maternal mortality in our state exclusive of Chicago, comprising over 400,000 deliveries, Dr. Charles Newberger reported that hemorrhage accounted for 33.7 per cent of 309 deaths. Even more important is the fact that we have the knowledge to prevent the vast majority of fatalities from this complication.

Undoubtedly complications of the placental stage are the most common causes of hemorrhage and shock. In the recent data on maternal deaths from shock in Massachusetts presented by Dr. Reid, the cause was uterine atony in 41 women, or 50 per cent of the total number, and trauma in 8, or 10 per cent. Furthermore, the placental stage may have been an important factor in the deaths from placenta previa, abruptio placentae, and placenta accreta. Thus, the placental stage played an important role in 3 of 4 of the patients who died of shock. I should like to comment briefly on the management of the placental stage of labor.

Excessive blood loss during the third stage of labor can be prevented by its proper management. For more than 20 years and in thousands of patients we have administered an oxytocic drug, ergonovine, during the delivery of the baby to expedite the normal mechanism of placental separation. This procedure has decreased significantly the average blood loss and the incidence of postpartum hemorrhage.

This artificial conduct of the placental stage may result in minor complications. The placenta may fail to separate completely or after separation it may be trapped in the lowermost portion of the contractile segment. When this happens it is our practice to explore the uterine cavity promptly to complete the separation if necessary or to ease out the separated placenta from the contracted zone which holds it. Such mannual explorations of the uterine cavity have resulted in no increased morbidity or other undesirable sequelae. Furthermore, we encourage our resident staff to explore the uterine

cavity whenever there is any question concerning the completeness of the placenta and when a fragment of placenta is missing. It has been my impression that the conservative teaching in our medical schools has made many physicians reluctant to explore the uterine cavity to the detriment of the patient.

A routine for the management of bleeding following delivery is highly desirable in a teaching institution for it indoctrinates young people to think logically and not to be stampeded by cataclysmic events. Thus, when abnormal bleeding occurs following the delivery of the baby the first thought in the mind of the doctor should be the proper provision for blood replacement. Fluids should be started promptly, blood for matching obtained from the patient and blood for replacement made available. How easily these practical routines are carried through prophylactically and how fouled up they can become in the face of an emergency! If bleeding begins prior to delivery of the placenta and a nontraumatic expression does not deliver it, manual exploration and removal are indicated. Bleeding following the expulsion of the placenta calls for a systematic examination of the entire reproductive tract for trauma, fragments of placenta, myomas, or accumulated clots, including the visualization of the entire vagina and cervix. Bleeding sources should be ligated and trauma repaired by suture. It is only then that a second dose of an oxytocic drug should be administered.

We believe, as does Dr. Reid, that uterine atony is usually the result of some underlying cause and rarely the result of an inherent deficiency of the uterine musculature. Furthermore, we, too, believe that there is still a place for a correctly placed uterine pack, although it is rarely indicated today. We must recognize, however, that if it proves ineffective it is folly to remove and replace it, for the patient is served better by the removal of the uterus. It is far, far better to have a living patient without her uterus than to bury her with the uterus inviolate.

It is indeed timely to have Dr. Reid bring to our attention the unnecessary loss of life from shock and hemorrhage in pregnancy. All of us, the teacher in his ivory tower and the physician in the small community should review his thinking so that each can lend a hand in tackling this major problem in our specialty.

DR. WILLIAM F. MENGERT.—I am certainly in agreement with Dr. Reid's general philosophies with regard to blood replacement. I feel that blood transfusion has saved more maternal lives, reduced or avoided more morbidity, and generally has been more beneficial than any measure or drug introduced into obstetrics during the last twenty-five years.

My personal experience with inversion of the uterus may be interesting to you. During my 14 years at the University of Iowa, there were 2, one chronic and one acute. The latter patient died. During nearly 12 years at Parkland Hospital we encounterd 3 acute inversions. Two were produced by the same practitioner. We replaced each uterus and both patients survived. The third patient was delivered by a midwife and was dead on arrival. Obviously, the unusual implantation of the placenta at the very top of the uterine cavity must have been a predisposing factor in production of this accident. On the other hand, the accident is almost always iatrogenic. For many years, when addressing audiences of general practitioners on this subject, I have asked for a show of hands of all those who have seen acute puerperal inversion of the uterus. Invariably, from 10 to 20 per cent of the audience responds.

Dr. Reid touchês briefly on the supine hypotensive syndrome and states this "does not represent a state of deterioration similar to shock" since "the symptoms are readily relieved by placing the patient on her side." Moreover, he feels these hypotensive episodes "should perhaps not be regarded as a form of shock, but rather designated syncopal attacks of pregnancy of neurogenic origin." We found that patients exhibiting this state experience a fall in systolic blood pressure, a decrease in pulse pressure, an elevated pulse rate, become cold, clammy, and break out in perspiration. I have seen the systolic blood pressure decrease to zero. The reaction requires 3 to 5 minutes to develop but can be immediately

corrected by placing the patient on her side. Dr. Reid does not believe this is shock because they can be so relieved. When we first began to seek the cause of this startling phenomenon I, like Dr. Reid, believed it was neurogenic. After we stimulated some nerves in dogs and found not decrease, *but elevation* of the blood pressure, I was shaken in this belief. When I compressed digitally the inferior vena cava below the renal veins at the time of cesarean section in each of 2 women and reproduced the syndrome, we thought we were producing cardiac failure by preventing return of the large quantities of blood combined in the uterine circulation and in the lower half of the body. Now Dr. Reid tells us I was stimulating nerves. I would greatly appreciate having Dr. Reid, in his discussion, explain the nervous mechanisms invoked by occlusion of the vena cava.

In passing, I would like to mention a clinical stunt which has been invaluable to me. If a laboring patient who has recently received spinal or saddle block anesthesia goes into an acute hypotensive episode, I turn her on either side before administering a pressor drug. Generally the pressure speedily returns to normal.

DR. ALFRED K. KOBAK.—I would like first to make a few comments on inversion of the uterus. When manual replacement of the uterus is not easily accomplished it is unsafe to persist in attempting it. When replacement is difficult I would like to recommend, based on personal experience, that the uterus if prolapsed be replaced in the vagina and the vagina all around the inverted uterus be tightly packed, with emphasis on the pressure upward toward the abdominal cavity. Thus a T-binder pressing upward upon the vulva is also helpful. In the meantime the important phase of management is to overcome the shock.

Upon listening to a dissertation on obstetrical shock I was surprised and puzzled to find a significant part of the paper devoted to the discussion of the extraperitoneal cesarean section. Very few obstetricians in the Chicago area employ the extraperitoneal cesarean technique when confronted with dystocia and infection. In the October, 1954, number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY there appeared three interesting articles dealing with the extraperitoneal approach in extraction of the baby. Every obstetrician, especially those still using this technique, should read these three articles in order to appreciate the present trends in choice of cesarean procedure when sepsis is a menacing factor. J. N. Connell, reviewing the maternal mortality at the Margaret Hague Hospital, cited a death from puerperal infection that followed an extraperitoneal cesarean section. Atherton and Williamson compared the results of 68 extraperitoneal cesarean sections with those of a similar number of low cervical transperitoneal procedures performed upon parturients who were potentially or frankly infected at that time. They very definitely demonstrated that there could be no doubt about the superiority of the simpler low cervical procedure. In the extraperitoneal group the morbidity was higher and there was one case of cervicovesical fistula and one case where the bladder was severed from the urethra. The third article was a case report describing a bladder avulsion as a complication in the performance of the extraperitoneal section. We now have a series of well over 400 cases where the simple low cervical cesarean section, together with the use of antibiotics and/or blood replacement as a feature addition, was used in cases having a septic background. We have had only one death which occurred in a patient who had diabetes mellitus, and who weighed over 300 pounds. She was not in labor. There was no peritonitis but she did have an infection that involved the surgical incision. As evidence of our confidence in our method of procedure we have had many frankly infected cases, including one patient with a temperature of over 103° F., who had a positive culture of *Streptococcus hemolyticus* in the amniotic fluid, and placentitis.

DR. REID (Closing).—The decision to utilize the extraperitoneal cesarean section in cases of trial labor with its constant threat of infection was precipitated by the discouraging results obtained from the last 100 transperitoneal lower segment cesarean sections performed prior to the introduction of chemotherapeutic agents. There were 4 deaths from peritonitis.

These fatal cases were not grossly infected at the time of operation, nor did their predelivery course differ in any respect from that of the patients who recovered. While it is readily granted that these fatal cases might not have been lost with present-day antibiotic agents, it is a disturbing fact that an increasing number of pathogenic organisms are being encountered in medical and surgical conditions which are resistant to known antibiotics. It is reasonable to suspect that the same will apply to the obstetrical patient. Consequently, it seems logical to avoid contamination of the peritoneal cavity at cesarean section in the potentially infected patient.

Some concern over the technique of the operation usually enters any discussion of the pros and cons of the value of extraperitoneal cesarean section. With our residents performing the majority of operations, in the last 200 cases extending over a ten-year period, the bladder has been traumatized in 5 per cent of the cases and the peritoneum buttonholed and closed immediately in 25 per cent of the cases. The latter is regarded as giving the end result of the Smith exclusion operation. In every instance the bladder healed promptly. In other words, there were no postoperative sequelae and the convalescence of these patients was conspicuous by the absence of distention and discomfort. During this 10 year period no uterus was removed at the time of cesarean section for infection alone. An equally safe operation which requires no greater time or technical skill than the transperitoneal lower segment cesarean section is the Smith exclusion operation. This procedure is a modification of the older Kehrer type of cesarean section, developed near the end of the last century. This procedure excludes the lower segment, prevents contamination of the peritoneal cavity when the uterus is open, and allows drainage of the potentially infected area.

What we have tried to point out in dealing with the elimination of traumatic pelvic delivery is that the incidence of primary cesarean section after a trial labor is higher when the transperitoneal cesarean section combined with antibiotic agents is the procedure of choice rather than the extraperitoneal type. One is forced to question whether the difference in the incidence of primary cesarean section was influenced by the fear of peritonitis in such cases. If this is true, it follows that a few cases could have been safely delivered by the pelvic route if they had been given additional labor.

Certainly Dr. Mengert has made significant contributions in the elucidation of the syndrome of postural hypotension in the pregnant patient. Whether the term "obstetrical shock" should be applied to this phenomenon is debatable.

ANEURYSMS COMPLICATED BY PREGNANCY

Part I. Aneurysms of the Aorta and Its Major Branches

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IMPROVED care and management of the parturient have resulted in a gratifying reduction in the maternal mortality rate. This has been accomplished primarily by a marked decrease in deaths due to purely obstetrical causes, but those due to nonobstetrical factors have not demonstrated a similar improvement. This emphasizes the necessity of directing attention to the latter group. With increased knowledge and awareness, the obstetrician in cooperation with the internist has been able to decrease the maternal mortality due to cardiac disease, diabetes, and other complications responsive to modern therapeutic regimes. However, there are other nonobstetrical abnormalities which are almost invariably fatal. This may be attributed largely to an almost universal lack of suspicion of their presence in conjunction with pregnancy so that the true diagnosis is made too frequently at postmortem examination. Furthermore, there is little clinical consciousness of these entities in pregnancy since scant attention is given to them in obstetrical teaching[1-3] and literature. This is unfortunate, since some of these are amenable to correction either before or during pregnancy. Greater awareness will lead to their earlier diagnosis and treatment with resultant improvement in maternal salvage.

Aneurysms constitute one of these nonobstetrical abnormalities which have not received adequate attention despite the fact that rupture during pregnancy is associated with a maternal mortality varying from 40 to 100 per cent. Although rupture of an aneurysm most commonly occurs after the age of 40, it may happen during the childbearing period and complicate pregnancy. Furthermore, the various clinical pictures produced by ruptured aneurysms simulate more obvious obstetrical complications. As a result, the treatment instituted is generally not directed toward the actual defect.

The purpose of this paper is to stimulate an awareness and develop a clinical consciousness of the coexistence of aneurysms of the arterial system and pregnancy, so that early and adequate therapy may be instituted. Hence, this publication will consider aneurysms of the aorta and its abdominal branches, and a companion paper will discuss cerebral aneurysms.

This report is based upon 75 cases of aneurysm of the aorta and 50 cases of aneurysm involving the major branches of the abdominal aorta culled from the literature (Tables I to IV). Two additional cases of saccular aneurysm

TABLE I. CASES OF SACCULAR ANEURYSM OF THE AORTA AND PREGNANCY REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE	OUTCOME
Adams[16]	1859	40	Not stated	Seventh month	Died
Cazeaux[17]	1868	40	iii	Labor	Died
Cleisz and Powilewicz[18]	1920	27	0	Unruptured	Lived
Commandeur[19]	1909	32	vii	Unruptured	Lived
Daly[20]	1924	Not stated	Multip-ara	Unruptured	Lived
	1924	Not stated	Multip-ara	Unruptured	Lived
Devilliers[21]	1863	38	vi	Ninth month	Died
Dominquez[22]	1911	Not stated	0	Unruptured	Lived
Goldstein[23]	1949	17	Not stated	Eighth month	Died
Hamilton and Thomson[24]	1941	35	Not stated	Unruptured	Lived
	1941	Not stated	Not stated	Unruptured	Lived
	1941	Not stated	Not stated	Unruptured	Lived
Hellman[25]	1955	Not stated	Not stated	Unruptured	Died
Hendry[26]	1923	Not stated	Not stated	Fifth postpartum day	Died
Hirst[27]	1895	Not stated	Not stated	Unruptured	Lived
Klages[28]	1912	27	0	Ninth month	Died
Kuchenmeister[29]	1867	26	Not stated	Unruptured	Lived
Mace and Monier-Vinard[30]	1906	29	iii	Unruptured	Lived
Rizzoli[31]	1908	Not stated	Not stated	Advanced pregnancy	Died
Tissier[32]	1908	26	0	Unruptured	Lived
Van Nest[33]	1925	48	xiv	Second month post partum	Died
	1925	Not stated	iv	Unruptured	Lived
Vander Veer and Kuo[34]	1950	Not stated	Not stated	Unruptured	Lived
Vinay[35]	1892	Not stated	Not stated	Labor	Died
Vozza[36]	1931	Not stated	Not stated	Unruptured	Lived
Walthard[37]	1913	Not stated	viii	Eighth month	Died
	1913	Not stated	Multip-ara	Unruptured	Lived
Present Authors	1956	30	ii	Fifth postpartum day	Died
	1956	35	iv	Abdominal hysterectomy first trimester	Lived

TABLE II. CASES OF DISSECTING ANEURYSM OF THE AORTA AND PREGNANCY REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE	OUTCOME
Anderson[38]	1949	35	v	Eighth month	Died
Berkhan[39]	1864	23	Not stated	Fourth month	Died
Billinghurst[40]	1943	23	0	Ninth month	Died
Bohm[41]	1930	31	0	Sixth postpartum day	Died
Bohnen[42]	1927	26	ii	Ninth month	Died
Elliotson[43]	1832	Not stated	Not stated	Seventh month	Died
Furman, Kennedy and Daniel[44]	1952	27	i	At two and one-half months	Lived
Goebel[45]	1936	30	i	Eighth month	Died
Griffiths, Hayhurst and Whitehead[46]	1951	34	iv	Fourth postpartum day	Died
Gutner[47]	1933	28	i	Term	Died
Heinricius[48]	1883	38	iii	Labor	Died
Heller[49]	1936	29	i	Forty-fifth day post abortion	Died
Henely[50]	1951	46	i	Ninth month	Died
Hickey[51]	1953	29	Not stated	Eighth month	Died
Johnson and Frank[52]	1947	34	Not stated	At eight and one-half months	Died
Katz[53]	1922	25	ii	Term	Died
	1921	33	Multipara	Fifth month	Died
Kaufmann[54]	1922	38	Not stated	Labor	Died
Kinney, Silvester and Levin[55]	1945	23	0	Last trimester	Died
Klotz and Simpson[56]	1932	39	Not stated	Sixth month	Died
	1932	23	Not stated	Eighth month	Died
Kosminski[57]	1896	30	i	Labor	Died
Lideboon and Bouder[58]	1949	23	Not stated	Not stated	Died
Mote and Carr[59]	1942	32	i	At four and one-half months	Lived (died two years and ten months later)
Mandel, Evans and Walford[60]	1934	20	0	At four and one-half months	Died
Millew[61]	1936	22	0	Term	Died

TABLE II—CONT'D

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE	OUTCOME
Norris[62]	1934	32	Not stated	Fourth month	Died
Palmer and Mathisen[63]	1946	29	Not stated	At five and one-half months	Died
Paulin and McGeachy[64]	1937	34	v	At five and one-half months	Died
Rosenthal[65]	1955	43	v	Eighth month	Died
Schaefer[66]	1938	44	0	Immediately post partum	Died
Schnitker and Bayer[67]	1944	22	0	Twelfth day post partum	Died
Sebold[68]	1916	36	i	At eight and one-half months	Died
Sichel, Nohlgren and Muehleck[69]	1954	35	ii	Fifth day post partum	Died
Spenser[70]	1952	32	Not stated	Eighth month	Died
Strassmann[71]	1922	25	i	Term	Died
Stratham[72]	1835	38	Not stated	Seventh month	Died
Vallhov[73]	1952	28	ii	Fifteenth day post partum	Died
Van Bouwdijk Bastiaanse[74]	1954	30	i	At seven and one-half months	Died
Vander Veer and Kuo[75]	1950	26	Not stated	Eighth month	Died
Von Bostrum[76]	1887	37	Multipara	Labor	Lived (died five and one-half months post partum)
Von Recklinghausen[77]	1865	Not stated	Not stated	Three weeks post partum	Died
Uebermuth[78]	1933	36	vii	Term	Died
Walter[79]	1902	38	v	Seventh postpartum day	Died
Weil, Yoder and Bachand[80]	1953	42	iii	Ninth month	Died
Weisswanger[81]	1903	30	i	Ninth month	Died
Wolff[82]	1933	26	Not stated	Labor	Died

of the aorta are being reported for the first time. One of these was in a patient who had a hysterectomy five years after a therapeutic interruption of pregnancy and tubal ligation for a fusiform aneurysm of the aorta. The second case is reported in greater detail.

TABLE III. CASES OF SPLENIC ANEURYSMS AND PREGNANCY REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE	OUTCOME
Bauer and Appelbach[83]	1932	24	Not stated	Eighth month	Died
Bohler[84]	1933	27	iii	Seventh month	Died
Chalmers[85]	1949	26	ii	Term	Died
Cosgrove, Watts and Kaump[86]	1947	29	Not stated	Fifth month	Died
	1947	29	Not stated	First postpartum day	Died
Danforth[87]	1948	28	ii	Seventh month	Died
DeVink and van der Linde[88]	1950	32	ii	Eighth month	Died
Gallagher and Hudson[89]	1954	32	Not stated	Fifth month	Lived
Gillam[90]	1942	26	0	Eighth month	Lived
Guy[91]	1939	25	Not stated	Fifth month	
Haberda[92]	1922	23	Not stated	Labor	Died
Heuveldop[93]	1934	38	ii	Eighth month	Died
Koliski[94]	1922	29	Not stated	Labor	Died
Lennie and Sheehan[95]	1942	30	iii	At seven and one-half months	Died
	1942	30	i	At seven and one-half months	Died
Lundwall and Godl[96]	1923	29	i	Term	Died
Mayer[97]	1928	27	iii	Term	Died
McLeod and Maurice[98]	1940	22	i	Sixth month	Lived
Nodes and Hinds[99]	1900	33	vi	Term	Died
Ogden[100]	1948	25	ii	Eighth month	Died
Ostling[101]	1938	21	i	Seventh day post partum	Died
Remmelts[102]	1928	38	ix	Term	Died
Saenger[103]	1926	40	ix	Seven and one-half months	Died
Sered and Steiner[104]	1935	30	iii	Term	Died
Sheehan and Falkiner[105]	1948	26	ii	Eighth month	Died
Smith[106]	1911	35	Not stated	Term	Died
Specken and de Bruyn[107]	1950	33	i	Labor	Died
Tennent and Starritt[108]	1950	36	ix	Sixth month	Died
Tomsykoski, Stevens, Izzo and Rodriques[109]	1953	41	ii	Term	Died

TABLE III—CONT'D

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE	OUTCOME
Toes[110]	1956	22	0	Fifth postpartum day	Died
Van Rooy[111]	1927	38	xi	Term	Died
Wesenberge[112]	1912	32	iv	Seventh month	Died
Yolland[113]	1925	27	i	Term	Died
Zummo, Williams and Uzanski[114]	1954	33	ii	Term	Died
	1954	32	0	Labor	Died

TABLE IV. CASES OF RENAL ANEURYSMS AND PREGNANCY REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	TIME OF RUPTURE OR DIAGNOSIS	OUTCOME
Burt, Johnston, Silverthorne, Lock, and Dickerson[115]	1956	28	x	Thirty-first week	Lived
Chisholm[116]	1926	28	0	Seventh month	Died
Hack[117]	1953	33	iii	Thirtieth week	Died
Lennie and Sheehan[118]	1942	24	v	Thirty-sixth week	Died
	1942	28	ii	Twenty-ninth week	Died
Low[119]	1944	35	ii	Term	Died
Ostling[120]	1938	24	0	Thirty-eighth week	Died
Ward and Martins[121]	1956	Not stated	Not stated	Not stated	Died
Wilson[122]	1945	25	Not stated	Term	Died
				Seventh month	Died
Zummo, Williams and Uzanski[123]	1952	24	0		

Case No. 38409, S. P., a 30-year-old Negro woman, para i, gravida iii, registered in the Kings County Hospital, State University Obstetrical Clinic, on Sept. 13, 1951. Her last normal menstrual period had occurred on June 5, 1951, and the expected date of confinement was March 12, 1952.

The history disclosed that she had had rheumatic fever at the age of 12. The first pregnancy in 1947 was complicated by bronchopneumonia and hypertension. X-rays taken at that time showed hilar adenopathy with fullness of the left hilar region in addition to a resolving bronchopneumonia. This pregnancy terminated with the delivery of a stillborn infant.

In 1949, at another hospital, following an uneventful antenatal course, she was delivered prematurely of a 2,240 gram infant. No chest x-rays were taken at that time.

During the present pregnancy, laboratory findings at her first outpatient visit showed a negative blood Wassermann test blood type A positive, and blood pressure of 170/105. A mediastinal opacity was demonstrated by routine chest x-ray.

The patient was hospitalized in order to evaluate further the mediastinal mass. Laboratory study in the hospital showed hemoglobin 13 Gm. (Sahli), red blood count 3.9 million, white blood count 10.9 thousand, hematocrit 40 per cent, peripheral smear normal, bone marrow smear normal, urinalysis essentially normal; tuberculin test negative at 1:1,000 dilution;

blood chemistry determinations, uric acid 2.2 mg. per cent, alkaline phosphatase 4.9 mg. per cent, total proteins .7 mg. per cent, albumin-globulin 3.5/3.2. The electrocardiographic studies were within normal limits. X-rays including posteroanterior view, cardiac oblique, and barium swallow were interpreted as showing a mediastinal mass, the nature of which could not definitely be determined. The patient was discharged from the hospital, to be followed in the outpatient department with a tentative diagnosis of aortic aneurysm or mediastinal tumor. While in the hospital her blood pressure had returned to normotensive levels of 120/80 and was stabilized at this level throughout the remainder of the antepartum period.

She was readmitted on Feb. 19, 1952, in active labor. Three hours later she was delivered by elective outlet forceps of a 2,750 gram living child under pudendal block and nitrous oxide-oxygen anesthesia.

Immediately post partum the blood pressure rose to 160/100 but she was normotensive 24 hours later. On the morning of the fifth postpartum day while waiting to be discharged, she stated that she had some vague back pain. This was followed in two hours by the sudden onset of palpitations, dizziness, and collapse. The pulse and blood pressure were unobtainable and five minutes after the onset of the acute episode she was pronounced dead.

Relevant Autopsy Findings.—The right pleural cavity contained approximately 1,500 c.c. of grossly bloody material and the left about 400 c.c. of yellow clear fluid. The left lung was partially collapsed by a huge aneurysmal diatation of the thoracic aorta which extended from its origin to the right pleural cavity. In addition, there was a transverse tear of the posterior aspect of the intima measuring 0.5 cm. This extended through the media and was limited by the adventitia. Dissection continued caudad within these layers to the origin of the celiac axis. At this point perforation of the adventitia had occurred and the hemorrhage extended retroperitoneally into the pelvis.

Microscopic Findings.—The intima was unevenly widened by masses of hyaline fibrous tissue with focal areas of a more cellular fibrous and a looser, blue, finely fibrillar type of fibrous tissue. Some small cystic mucinous changes were present. There were a few small foci of calcification noted. The media was permeated by numerous small blood vessels. The usual architecture was disrupted by irregular areas of fibrosis. There were diffusely scattered microcystic degenerative changes of the muscular and elastic elements. In some areas the boundary demarcating media and intima was lost by virtue of fibrosis and cystic changes.

The vasa vasorum showed cuffing with many large plasma cells and lymphocytes. These vessels had widened walls and showed proliferation of the endothelium.

Pathogenesis and Pathological Anatomy.—Aneurysms of the thoracic aorta usually develop as a result of weakening of the medial layer with subsequent dilatation of the vessel wall. When this process involves the entire circumference uniformly a fusiform aneurysm results. A saccular aneurysm forms if there is a focal area of weakness. The tension of normal blood flow past the weakened area produces the dilatation. Slowing of the circulation within the enlarging saccular aneurysmal cavity results in thrombus formation. Eventually, the wall becomes composed purely of fibrin and adventitia. Rupture most commonly occurs by erosion of the sac wall or occasionally secondary to the formation of a dissecting aneurysm as in the case herein reported.

Syphilitic mesoaortitis is the most common cause of saccular aneurysm during the reproductive years and was present in 7 cases. Infected embolus secondary to rheumatic heart disease or subacute bacterial endocarditis was the etiological agent in three cases, and trauma in one. In the remaining cases, no definite cause was stated but, in all probability, syphilis was the responsible factor (Table V).

A detailed discussion of the various pathological aspects of dissecting aneurysm is not within the scope of this paper. This has been well described by various authors.[4-7] Necrosis of the media was noted in 19 instances, congenital defects in 10, arteriosclerosis in 6, syphilis in 2, and infected embolus in one instance (Table VI).

TABLE V. ETIOLOGICAL FACTORS IN 112 CASES OF ANEURYSM OF THE AORTA AND THE SPLENIC ARTERY IN PREGNANCY

LOCATION OR TYPE	TOTAL CASES	SYPHILIS	MYCOTIC	ARTERIOSCLEROTIC	MEDIAL NECROSIS	CONGENITAL	TRAUMA	NOT STATED
Aortic								
Fusiform or saccular	29	8	3	0	0	0	1	17
Dissecting*	48	2	1	6	19	10	0	14
Splenic	35	0	2	0	0	11	0	22

*Occasionally more than one factor incriminated.

TABLE VI. TIME OF RUPTURE IN RELATION TO PERIOD OF GESTATION IN 108 CASES OF AORTIC ANEURYSM OR ANEURYSM OF THE MAJOR BRANCHES

LOCATION OR TYPE	TOTAL CASES	TRIMESTER			LABOR AND FIRST 24 HOUR PERIOD	DAY POST PARTUM			
		1ST	2ND	3RD		2-4	5-9	10 OR MORE	NOT STATED
Aortic									
Fusiform or saccular*	12	0	1	6	2	0	2	1	0
Dissecting	48	1	8	23	6	1	4	4	1
Splenic	35	0	5	23	6	0	1	0	0
Renal	10	0	0	9	0	0	0	0	1
Iliac†	3	0	1	1	0	0	0	1	0
Grand Total	108	1	15	62	14	1	7	6	2

*Seventeen saccular aneurysms did not rupture during pregnancy.
†Two iliac aneurysms did not rupture during pregnancy.

Aneurysms of the branches of the abdominal aorta are either developmental, mycotic, or arteriosclerotic in origin. The great majority of those encountered during the childbearing age are, as expected, congenital in origin. Septic aneurysms occur most commonly during the course of bacterial endocarditis or thrombophlebitis. This type was found in only 2 cases of splenic aneurysm, is rare during the childbearing age, and accordingly this was not the responsible etiological factor in any of the cases of this series.

Predisposing Factors.—

Anomalies of the Aorta: The presence of a congenital defect of the aorta predisposes to the development of a dissecting aneurysm. This was present in 10 cases; 2 were associated with aortic hypoplasia and 8 with coarctation. Although 98 cases of coarctation of the aorta complicated by pregnancy have been reported, 13 of these terminated fatally, 8 due to rupture of the artery secondary to a dissecting aneurysm, and the remaining 5 to other causes. On superficial examination, this high incidence appears to indicate that pregnancy increases the frequency of this complication. However, Abbott and Hamilton[8] noted that spontaneous rupture of the aorta occurred in 38 of their 200 cases of coarctation. Similar observations have been reported by other investigators.[5, 9] Therefore, the incidence of dissecting aneurysms in cases of coarctation is no greater during pregnancy than in the nonpregnant state.

Klotz and Simpson[56] found medial cystic necrosis (similar to Erdheim's disease) to be present in their cases of coarctation with ruptured dissecting aneurysms. In all probability, this would have been noted more commonly if complete descriptions of the pathologic lesions were available or if more careful pathological studies had been performed.

Hypertension: The presence of hypertension was noted in 19 of the 40 cases of dissecting aneurysm where the blood pressure was recorded. A high incidence of associated hypertension with dissecting aneurysm has been noted even in the nonpregnant state by Sherman,[5] McGeachey and Paulin,[64] and

other observers.[4, 67] However, the frequency of hypertension in cases of dissecting aneurysm during pregnancy is not as great as it is in individuals over 40 years of age. Hypertension does not play a primary role in the formation of a dissecting aneurysm, but is a subordinate or precipitating factor influencing the course of dissection through the underlying areas of medial necrosis of the aorta. It has been shown experimentally[56] that the normal aorta does not rupture until pressures greater than 2,000 mm. of mercury have been exerted. It is therefore highly unlikely that a normal aorta would rupture at the levels encountered in the hypertensive or toxemic states. Elevated tension will also precipitate rupture of aneurysms of the aortic branches.

Time of Rupture.—Rupture of aneurysms of the abdominal aorta and its branches is rare in the first trimester and gradually increases in frequency, reaching a peak during the third trimester and declines thereafter. Contary to what one would expect, the stress of labor is a relatively benign factor in the causation of this catastrophe. Thus, only 6 of the 48 dissecting aneurysms, 6 of the splenic, and 2 of the 29 saccular aneurysms ruptured during labor or in the immediate 24 hour period following delivery. No renal or iliac aneurysm ruptured during this period as noted in Table VI.

This accident occurred most commonly during the latter months of pregnancy. This parallels the physiologic increase in cardiac output and blood volume during pregnancy and the hemodynamic alterations appear to be the most significant factor in the precipitation of rupture. Increasing intra-abdominal pressure due to an enlarging uterus and changes in abdominal tension during and following delivery also may enhance rupture of abdominal aneurysm. Rupture in the puerperium probably occurs as a result of further weakening of the wall of the aneurysm by the hemodynamic changes of the early puerperium, so that it cannot withstand the tension of the normal blood flow.

TABLE VII. AGE DISTRIBUTION OF 127 CASES OF ANEURYSM OF THE AORTA OR ITS MAJOR BRANCHES DURING PREGNANCY

LOCATION OR TYPE	TOTAL CASES	AGE							
		15-19	20-24	25-29	30-34	35-39	40-44	45 AND OVER	NOT STATED
Aortic									
Fusiform or saccular	29	1	0	5	2	3	2	1	15
Dissecting	48	0	8	11	13	10	3	1	2
Splenic	35	0	7	12	9	5	2	0	0
Renal	10	0	3	4	1	1	0	0	1
Iliac	5	1	1	2	0	1	0	0	0
Grand total	127	2	19	34	25	20	7	2	18

Clinical Features.—The exact incidence of rupture of aneurysms of the aorta and its abdominal branches during pregnancy cannot be evaluated since many are not diagnosed and others are recorded in the medical or surgical rather than in obstetrical statistics. However, this study indicates that the location and frequency of rupture of aneurysms during pregnancy are similar to those encountered in the general population. The most common site involved is the thoracic aorta; the splenic artery is next most frequent; and then thereafter there is a progressive decrease in incidence with the iliac vessels rarely the seat of rupture.

With the exception of saccular aneurysms, the majority encountered during pregnancy are congenital in origin. This is emphasized by the fact that

63.0 per cent of the patients whose ages were stated were less than 35 years of age (Table VII). Sixty-eight point two per cent of the patients whose parity was noted were multiparas (Table VIII).

TABLE VIII. PARITY IN 127 CASES OF ANEURYSM OF THE AORTA OF ITS MAJOR BRANCHES

LOCATION OR TYPE	TOTAL CASES	PRIMI-GRAVIDAS	PARITY	
			MULTIPARA	NOT STATED
Aortic				
Fusiform or saccular	29	4	12	13
Dissecting	48	9	24	15
Splenic	35	8	18	9
Renal	10	3	5	2
Iliac	5	4	1	0
Grand total	127	28	60	39

Signs and Symptoms.—

Saccular or fusiform aneurysm: These may or may not be symptomatic. The symptoms and findings are adequately described in standard medical textbooks.

Dissecting aneurysm: The clinical syndrome produced by dissecting aneurysm will vary greatly depending upon the site and degree of dissection and the organs involved. Most commonly there is excruciating precordial or upper abdominal pain with a rapid onset of collapse, loss of consciousness, and demise. If this is not immediately fatal and unconsciousness does not ensue, the pain increases in intensity and may be referred to an area varying from the shoulders to the thigh or groin, depending upon the extent of the aorta involved by the dissection. Narcotics fail to relieve the pain. Rarely pain may be absent. Difficulty in respiration may be encountered. Cerebral manifestations varying from disorientation to convulsive seizures or coma may be seen. Renal or gastrointestinal involvement may produce hematuria or melena.

The physical findings most commonly encountered are tachycardia, pyrexia, and tachypnea. Unlike the blood pressure in massive myocardial infarction, the blood pressure frequently remains the same as it had been prior to the rupture. Cardiac decompensation may result and other findings are dependent upon the organs involved.

Aortic branches: Rupture of an aneurysm of a branch of the abdominal aorta presents the picture of an acute abdominal catastrophe, namely, shock, acute condition of the abdomen, and evidence of intra-abdominal hemorrhage. This is indistinguishable from intraperitoneal bleeding from any other cause. However, early symptoms will aid in localizing the offending vessel.

With rupture of a splenic aneurysm, there is sudden severe pain in either the epigastric or left hypogastric region, and occasionally referred to the left shoulder. Nausea and vomiting may be present. At the onset, tenderness and muscular rigidity are limited to these areas. As hemorrhage continues and blood escapes into the general peritoneal cavity, the acute surgical abdominal crisis develops. These findings were noted in all the cases with splenic involvement.

The cardinal differentiating symptom in cases of rupture of a renal aneurysm is the onset of severe pain in the flank on the side of the vessel involved. As the hemorrhage progresses, signs of intra-abdominal bleeding ensue following perforation of the overlying peritoneum.

The earliest manifestation of rupture of an iliac aneurysm is low abdominal pain radiating to the groin and down the leg of the side affected. At this point a mass may be palpated in the broad ligament. Later, the mass may no longer be palpated since the overdistended broad ligament ruptures and the classical picture of massive intra-abdominal hemorrhage becomes apparent.

The diagnosis of abdominal aneurysms is most difficult. Prior to rupture, the patient is asymptomatic and occasionally the diagnosis is made accidentally by the discovery of a calcified shadow on a routine x-ray of the abdomen. The symptom of leakage of a small quantity of blood is not of diagnostic import per se, but after massive rupture the history aids in localizing the lesion. Because of their rarity, ruptured aneurysms are almost never considered in the differential diagnosis of obstetrical complications which produce a similar picture. The preoperative diagnosis is usually dependent upon the period of gestation. The most common preoperative diagnoses in cases of rupture of a splenic aneurysm were ruptured uterus or ablatio placentae (Table IX). In only 3 cases was disease of the spleen suspected. Even at operation the diagnosis was frequently incorrect as evidenced by the procedure performed, namely, hysterectomy, cesarean section, and exploratory laparotomy.

TABLE IX. PREOPERATIVE DIAGNOSIS AND THERAPY IN 35 CASES OF SPLENIC ANEURYSM IN PREGNANCY

	NUMBER OF CASES
Preoperative Diagnosis.—	
Not stated	3
None	6
Ruptured uterus	7
Ruptured viscus	1
Internal hemorrhage	5
Ruptured ectopic pregnancy	1
Ablatio placentae	7
Excessive sedation	1
Ruptured spleen	3
Pulmonary embolism	1
Total	35
Therapy.—	
Not stated	2
None	22
Exploratory laparotomy	2
Cesarean section	4
Splenectomy	3
Abdominal hysterectomy	1
Vaginal hysterectomy	1
Total	35

Treatment.—All ruptured aneurysms of the thoracic aorta were treated medically and terminated fatally, with the exception of 3 cases of incomplete dissecting aneurysms. One[59] of these patients subsequently succumbed almost three years later, when dissection occurred through the adventitia.

The treatment for ruptured abdominal aneurysm is immediate surgical intervention and adequate blood replacement.

TABLE X. MATERNAL MORTALITY IN 127 CASES OF ANEURYSM OF THE AORTA OR ITS MAJOR BRANCHES

LOCATION OR TYPE	TOTAL CASES	MATERNAL END RESULTS	
		LIVED	DIED
Aortic			
Fusiform or saccular	29	17*	12
Dissecting	48	3	45
Splenic	35	3	32
Renal	10	1	9
Iliac	5	4†	1
Grand total	127	28	99

*Did not rupture.

†Two did not rupture, but both patients succumbed during attempts at surgical correction, one and eight months post partum.

Splenic aneurysms are treated by ligation of the involved vessel or splenectomy. Aseptic necrosis of the spleen has no deleterious effects. In renal cases, the vessel is ligated proximal to the aneurysm and nephrectomy performed if the patient's condition permits. In the latter months of pregnancy, cesarean section is usually necessary to facilitate exposure of the operative field.

Hysterectomy may be required to visualize rupture of an iliac aneurysm. This may be treated by proximal ligation and, if the patient's condition is satisfactory, arterioplasty is indicated when feasible. The necessity for immediate diagnosis and adequate surgery is emphasized by the fact that the only patients to survive rupture of splenic aneurysms were 3 so treated (Table X).

Comment

With modern advances in cardiovascular surgery, coarctation and saccular or fusiform aneurysms of the aorta have now become amenable to treatment. Once rupture has occurred, intervention becomes a desperate heroic measure invariably doomed to failure. The importance of diagnosis prior to pregnancy is not only academic but offers the only hope for decreasing the high maternal mortality resulting from rupture. Certainly operation is more advisable in the nonpregnant individual than in the pregnant state with its accompanying circulatory changes.

In this series surgical correction of a coarctation was performed in one patient early in pregnancy who subsequently developed a fusiform aneurysm at the point of anastomosis that ruptured in the third trimester. There are other reports[11, 12] of successful surgical correction during pregnancy, however. The surgical procedure selected depends upon the defect present.

Gore,[13] analyzing 32 cases of dissecting aneurysm in men under 40, noted an unusually large number of congenital abnormalities of the aorta. It is his feeling that a metabolic defect is present in the vessel wall. This is not demonstrable at birth but becomes evident later in life. The factors responsible for the changes other than aging are at present unknown and resemble similar changes seen in Marfan's disease. In his group, hypertension was seen in only 3 of the 32 cases reported. Schnitker and Bayer[67] proposed that the altered lipid metabolism in pregnancy may be the responsible factor for changes in the vessel wall, and experimentally have produced dissecting aneurysm in animals by high-cholesterol diets. Carr,[14] on postmortem material, has demonstrated lesions resembling medial cystic necrosis without dissection in pregnancy.

If these hypotheses are correct, it may very well be that the marked physiologic alterations of pregnancy enhance the development of metabolic changes in the vessel wall of susceptible individuals.

This may partially explain the fact that 50 per cent of dissecting aneurysms in women under the age of 40 have occurred during pregnancy. The factor precipitating rupture of the diseased vessel is probably the increased stress upon the vascular tree, produced by the greater cardiac output and volume and abetted in 47.5 per cent of the cases in this series by a complicating hypertension.

Hypertension at this age in either sex is uncommon. The increased incidence in this group of women is peculiar to pregnancy and usually denotes a coexisting pre-eclampsia or eclampsia. The already vulnerable vessel, barely maintaining itself under the increased circulatory load of pregnancy, may rupture upon the addition of the increased tension of pre-eclampsia.

Only by the development of a clinical consciousness that rupture of an aneurysm of the abdominal branches of the aorta can complicate pregnancy, and that it is best treated by immediate and adequate surgery, will a reduction of the maternal mortality from the magnitude herein reported be accomplished. The difficulty of arriving at a correct diagnosis prior to laparotomy is understandable. There are many obstetrical complications which simulate rupture, and these are more frequently encountered. In early pregnancy, it resembles ruptured ectopic gestation and in the later months it mimics ruptured uterus or premature separation of the placenta. If at laparotomy the more obvious diagnosis is not confirmed, then there should be no hesitancy in extending the incision and performing a thorough exploration, with particular attention directed toward possible sites of aneurysm formation.

Eight cases of nontraumatic splenic rupture,[15] in which the capsules were lacerated but no aneurysm demonstrated, have been reported. A higher salvage rate in this group as compared to the series of ruptured aneurysms is due to earlier diagnosis, a less fulminating course, and easier visualization at laparotomy. It is possible that these represent rupture of intrasplenic aneurysms and careful dissection of the vascular network might have disclosed the presence of the responsible lesion.

The mode of delivery is of practical importance only in cases of coarctation of the aorta, and fusiform or saccular aneurysm. In the others, the diagnosis is rarely made until after rupture has occurred.

In regard to coarctation, opinions vary. Some advocate vaginal, others abdominal delivery, and a third group advises therapeutic interruption of pregnancy. Although no statistically valid data can be derived from this study, it appears that labor per se plays a relatively insignificant role in the formation of dissecting aneurysms, but that altered hemodynamics is the important factor. Therefore, it appears that abdominal delivery offers little if any advantage over vaginal delivery.

The reported number of cases of coarctation complicated by pregnancy represents a small fraction of such cases. Certainly, in the vast majority of the unreported cases, delivery was uneventful by the vaginal route. The actual maternal mortality rate associated with coarctation is probably less than the 13.3 per cent reported in the literature.

Summary and Conclusions

1. An analysis of 29 cases of fusiform or saccular aneurysm of the aorta, 48 of dissecting aneurysm of the aorta, 35 of splenic, 10 of renal, and 5 of iliac, is presented. Two of the sacculated aneurysms are reported for the first time.

2. Most aneurysms encountered during the childbearing age are congenital in origin. Sacculated aneurysms are most likely syphilitic in etiology.

3. The change in hemodynamics is the most common factor predisposing to the rupture of an aneurysm during pregnancy. The frequency of rupture parallels the alterations in circulatory volume and cardiac output, reaching a peak in the third trimester.

4. Stress of labor plays a relatively minor role in the cause of rupture.

5. Hypertension is a precipitating rather than a predisposing factor in the causation of rupture.

6. The clinical features of ruptured aneurysm of the aorta are presented.

7. Surgical correction of sacculated or fusiform aneurysm of the aorta, or coarctation prior to pregnancy, at present offers the best hope of decreasing the maternal mortality associated with rupture of the aorta.

8. Rupture of an aneurysm of branches of the abdominal aorta produces the picture of an acute abdominal catastrophe, indistinguishable from intra-abdominal bleeding regardless of the cause.

9. The high maternal mortality which accompanies rupture of an aneurysm of a branch of the abdominal aorta may be reduced only by early diagnosis and adequate surgery.

10. An awareness that ruptured aneurysms do complicate pregnancy and are a cause of intraperitoneal hemorrhage will result in early diagnosis and adequate therapy.

11. The creation of a clinical consciousness that rupture of an aneurysm should have a place in the differential diagnosis of acute abdominal conditions is of value both preoperatively and during surgery.

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ANEURYSMS COMPLICATED BY PREGNANCY

Part II. Aneurysms of the Cerebral Vessels

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DESPITE a maternal mortality of more than 40 per cent associated with cerebrovascular complications of pregnancy, little attention has been focused upon this problem. The actual frequency of this disaster cannot be ascertained from the literature or personal experience, since the true diagnosis is often not established in patients who survive, and surprisingly is found at autopsy in many cases where the diagnosis was clinically unsuspected. Rarely is the aid of a neurologist sought, for most of the cases are erroneously diagnosed and treated as toxemias of pregnancy. The symptom complex of hypertension, convulsion, albuminuria, and coma is common to both eclampsia and cerebral complications of pregnancy. More frequent neurological consultation in "questionable" cases of toxemia would result in the correct diagnosis being made more often, which would not only supplement our diagnostic acumen, but also result in proper management.

Subarachnoid hemorrhage is the most common cerebrovascular complication encountered during pregnancy. The magnitude of the problem is obscured by inadequate and incorrect diagnosis, and the available data do not reflect the true incidence. Until recently, accurate diagnosis was merely academic, for no active therapy was available. Today, however, in many cases of subarachnoid hemorrhage secondary to rupture of a cerebral aneurysm definitive and successful surgical intervention is possible.

Ruptured cerebral aneurysm is a relatively rare complication of pregnancy, whose reported frequency will probably increase with more accurate diagnosis. Although there has been a considerable amount written concerning it, as a complication of normal pregnancy it has received relatively little attention. Most of the reports are to be found in the nonobstetrical publications and the subject is not discussed in the standard obstetrical textbooks.[1-3]

The present-day high maternal mortality associated with this complication can be reduced only through early recognition and adequate treatment. These are dependent upon an awareness on the part of physicians that ruptured aneurysms may occur during pregnancy. Knowledge of the clinical manifestations, prognosis, and treatment can be obtained only by a collective study of the cases reported to date, since no one institution has had sufficient experience.

This study is based upon 79 cases of probable or proved cerebral aneurysm. Seventy-seven were obtained from the literature and 2 additional cases from the Kings County Hospital of Brooklyn are reported for the first time (Tables I and II).

CASE 1.—No. 22461. E. R., aged 21 years, para iii, gravida iv, whose expected date of confinement was Sept. 1, 1953, was admitted to Kings County Hospital on May 10, 1953, in coma and having convulsive seizures. Physical examination showed a comatose young woman in opisthotonos and with marked rigidity of the lower extremities. The blood pressure varied from 120 to 200/80 to 100. The pulse was 100 per minute, temperature 102.8° F. The uterus was enlarged to the size of a 24 weeks' gestation. Deep tendon reflexes were absent. There were Babinski reflexes bilaterally. Spinal puncture was grossly bloody and the urinalysis showed 2 plus albumin and a trace of acetone. The impression at that time was ruptured cerebral aneurysm complicating a 24 weeks' gestation.

The patient responded to supportive therapy. Angiography on the sixth hospital day failed to demonstrate an aneurysm. The following day an exploratory craniotomy was performed and the source of bleeding was not located. On June 17, 1953, under local anesthesia, the internal carotid artery was ligated. The patient withstood the procedure without adverse effect. The blood pressure returned to normotensive levels and the albuminuria was not demonstrable after the fifth postoperative day. Despite no sequelae or evidence of fresh bleeding, it was deemed advisable to continue hospitalization until the normal termination of pregnancy.

At 5 A.M. on Aug. 30, 1953, she complained of "cramplike" abdominal and low back pain, and was delivered three hours later of a 3,317 gram infant over an intact perineum from the left sacral anterior position. The postpartum course was normal and she was discharged with her child on Sept. 13, 1953.

CASE 2.—H. V., 27 years of age, a primigravida, was admitted in coma to the Kings County Hospital on Nov. 5, 1953. The last menstrual period was March 16, 1953, and the expected date of confinement was Dec. 23, 1953.

The past history disclosed recurrent headaches which were relieved by aspirin. The antenatal course had been uneventful. At the last visit to her obstetrician, two days prior to admission, the blood pressure and urinary findings were within normal limits.

At 4 A.M., one and one-half hours prior to admission, the patient was awakened from sleep by a severe headache and within a few moments experienced generalized convulsions and became comatose.

Physical examination on admission showed a comatose white woman in opisthotonos, exhibiting decerebrate-like rigidity. The blood pressure was 120/70 and the pulse rate 110 per minute and regular. The pupils were fixed and did not react to light. Ophthalmoscopic examination showed several fresh, flamelike hemorrhages in the temporal area of the right fundus as well as papilledema of the right optic disc.

The size of the uterus was consistent with the period of gestation. The fetus was in the left occiput anterior position, and the fetal heart was audible in the left lower quadrant at the rate of 136 per minute. Urinalysis showed a trace of albumin. Supportive therapy was administered and neurological consultation was obtained.

The neurologist confirmed the diagnosis of ruptured cerebral aneurysm but in view of the patient's rapidly deteriorating condition he did not feel that a spinal tap was indicated to corroborate the diagnosis.

Forty-five minutes after admission, the patient died. Three minutes later a postmortem cesarean section was performed. At delivery the infant was in poor condition and the heart ceased to beat ten minutes later.

Consent for postmortem examination was not granted.

Location and Size.—Intracranial aneurysms most commonly arise at the angle of the bifurcation of the vessels of the circle of Willis or early in the proximal course of its branches. The next most common site, as shown by

TABLE I. CASES OF PROVED CEREBRAL ANEURYSM REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	GESTATION	DELIVERY	OUTCOME	SURGERY
Bell[17]	1951	Not stated	Not stated	Term	Cesarean section	Died	--
Brehm[18]	1951	33	0	Sixth month	Cesarean section	Lived	Seventh month
Christensen and Larsen[19]	1953	27	0	Term	Undelivered	Died	--
	1953	32	0	Seventh month	Undelivered	Died	--
	1953	24	0	Term	Not stated	Lived	--
Conley and Rand[20]	1951	26	0	Sixth month	Cesarean section	Lived	Sixth month
	1951	29	0	Immediately post partum	Spontaneous	Lived	--
de Carle[21]	1951	29	ii	Term	Cesarean section	Died	--
	1951	23	0	Eighth month	Cesarean section	Died	--
Decker and Rowe[22]	1953	21	0	Fourth month	Low forceps	Lived	Seventh month
Feldman, Gross, and Wimpfheimer[23]	1955	28	0	Eighth month	Cesarean section	Lived	Eighth month
Hamby[24]	1948	Not stated	Not stated	Ante partum	Not stated		--
	1948	Not stated	Not stated	Ante partum	Not stated		--
	1948	Not stated	Not stated	Post partum	Not stated	2 of these died	--
	1948	Not stated	Not stated	Post partum	Not stated		--
Hasset[25]	1953	37	iii	Thirty-fourth week	Cesarean section	Died	--
Herzig[26]	1948	34	i	Thirty-second week	Not stated	Died	--
Johnson[27]	1952	Not stated	Not stated	Not stated	Not stated	Died	--
	1952	Not stated	Not stated	Not stated	Not stated	Died	--
Kreeger and Pedowitz[28]	1955	28	0	Immediately post partum	Low forceps	Lived	--
Lazard[29]	1899	31	ii	Labor	Spontaneous	Died	--
Madow and Alpers[30]	1953	33	i	Eighth-month	Cesarean section	Died	Post partum
Olivecrona and Rives[31]	1948	29	Not stated	Seventh month	Not stated	Lived	Seventh month
Richardson and Hyland[32]	1941	38	v	Fourth month	Undelivered	Died	--
	1941	Not stated	Not stated	Not stated	Not stated	Died	--
	1941	Not stated	Not stated	Not stated	Not stated	Died	--

TABLE I—CONT'D

AUTHOR	YEAR	AGE	PARITY	GESTATION	DELIVERY	OUTCOME	SURGERY
Rhoads[33]	1947	Not stated	0	Third and fifth month	Undelivered	Died	--
Schwartz[34]	1951	23	Not stated	Eighth month	Postmortem section	Died	--
Speck[35]	1954	35	i	Fifth day post partum	Spontaneous	Lived	Eighteen days post portum
Stone[36]	1949	33	i	Thirty-seventh week	Cesarean section	Lived	Four weeks post partum
Strohschein and Suzuki[37]	1947	35	i	Term	Cesarean section	Died	--
Walton[38]	1953	40	Not stated	Twenty-sixth week	Undelivered	Died	--

Richardson and Hyland,[32] is at the bifurcation of the internal carotid artery. Other locations, less frequently found, are at the anastomosis of the vertebrals forming the basilar artery, or the internal carotid before its division, and the intracranial portion of the vertebrals.

Spontaneous subarachnoid hemorrhage may be primary or secondary. In the former, bleeding arises from a ruptured vessel in the subarachnoid space and may or may not involve the adjacent brain tissue. In secondary subarachnoid hemorrhage, the initial lesion is intracerebral bleeding with subsequent perforation through an area of encephalomalacia into the subarachnoid space.

Ruptured cerebral aneurysms give rise to primary subarachnoid hemorrhage and involve the cerebrum in the majority of cases. Richardson and Hyland found intracerebral hemorrhage present in 70.4 per cent of their cases of ruptured cerebral aneurysms. This intracerebral component probably results from the aneurysm being either partially imbedded or in close apposition to the cortex. Thus, ventricular hemorrhage may result and the findings simulate primary intracerebral hemorrhage. Only with careful dissection of the vascular supply of the brain may one demonstrate the ruptured aneurysm and differentiate secondary from primary intracerebral hemorrhage.

The congenital origin of cerebral aneurysms was realized as early as 1887 when Eppinger[4] suggested that they resulted from developmental defects in the vessel walls and called them berry aneurysms. Forbus,[5] in 1930, and Richardson and Hyland[32] in 1941 demonstrated a medial defect, the absence of the muscularis at the point of sacculation. Glynn,[6] however, maintained that the internal elastic membrane rather than the defective or absent muscularis was the factor responsible for the development of the aneurysm. Helpern[7] demonstrated microscopically that the wall of the aneurysm was almost devoid of both internal elastic membranes and muscular layer, and was composed only of intima and adventitia. Bremer[8] found by embryological studies that true congenital aneurysm lacked both media and internal elastica, and that these defects occur most frequently at the bifurcation of the major cerebral vessels. The ages of the patients in this series further emphasize the congenital nature of the lesion (Table III).

Signs and Symptoms.—Aneurysms, prior to rupture, are usually asymptomatic. With rupture, free blood in the subarachnoid space produces the characteristic features of meningeal irritation. The earliest and most common

TABLE II. CASES OF PROBABLE CEREBRAL ANEURYSM REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE	PARITY	GESTATION	DELIVERY	OUTCOME	SURGERY
Bell[39]	1951	36	ii	Immediately post partum	Not stated	Died	--
Chesley[40]	1951	25	0	Labor	Low forceps	Died	--
Conley and Rand[41]	1951	21	0	Sixth month	Low forceps	Lived	--
	1951	33	Multipara	Term	Spontaneous	Died	--
	1951	26	Multipara	Labor	Cesarean section	Lived	--
	1951	34	Multipara	Labor	Cesarean section	Lived	--
	1951	32	0	Seventh month	Cesarean section	Lived	--
Dahl[42]	1946	34	Not stated	Labor	Spontaneous	Lived	--
Fleming and Mauzy[43]	1956	30	i	Twenty-eighth week	Low forceps	Lived	--
Flexner and Schneider[44]	1936	20	0	Second week post partum	Low forceps	Lived	--
Garber and Maier[45]	1948	26	0	Eighth month	Cesarean section	Lived	--
	1948	26	Multipara	Term	Cesarean section	Lived	--
	1948	24	0	First day post partum	Low forceps	Lived	--
Gershenfeld and Savel[46]	1950	24	0	Third day post partum	Spontaneous	Lived	--
Guttmacher[47]	1955	Not stated	Not stated	Not stated	Not stated	Not stated	--
Hall and Corradini[48]	1952	Not stated	Multipara	Labor	Spontaneous	Died	--
	1952	25	0	Labor	Midforceps	Lived	Fourth day post partum
Johnson[49]	1952	26	0	Labor	Low forceps	Lived	--
	1952	26	i	Eighth day post partum	Low forceps	Lived	--
	1952	24	0	Twenty-third day post partum	Low forceps	Lived	--
	1952	36	0	Twentieth week	Cesarean section	Lived	--
Kreeger and Pedowitz[50]	1955	35	0	Thirty-fourth week	Low forceps	Lived	--
	1955	25	i	Fifth day post partum	Low forceps	Lived	--
	1955	34	ii	Fifth day post partum	Cesarean section	Lived	--
Masten[51]	1935	Not stated	Not stated	Eighth month	Undelivered	Died	--
Millen[52]	1956	35	Multipara	Second trimester	Low forceps	Lived	--
	1956	45	0	Immediately post partum	Cesarean section	Lived	--

TABLE II—CONT'D

AUTHOR	YEAR	AGE	PARITY	GESTATION	DELIVERY	OUTCOME	SURGERY
Moskowitz and Schneider[53]	1943	25	0	Labor	Undelivered	Died	--
	1943	26	Multipara	Second hour post partum	Spontaneous	Lived	--
	1943	25	0	Immediately post partum	Spontaneous	Died	--
Ohler and Hurwitz[54]	1932	27	Not stated	Seventeen days post partum	Spontaneous	Died	--
Parks and Pearson[55]	1943	22	v	Term	Spontaneous	Died	--
Ramstadt[56]	1948	37	ii	Ninth month	Cesarean section	Died	--
Rhoads[57]	1947	27	Not stated	Ninth day post partum	Spontaneous	Lived	--
Russell[58]	1933	22	0	Third month	Not stated	Not stated	--
	1933	Not stated	0	Seventh month	Not stated	Not stated	--
	1933	24	0	Labor	Low forceps	Lived	--
	1933	Not stated	0	Term	Not stated	Not stated	--
	1933	34	Multipara	Eight hours post partum	Spontaneous	Died	--
Schwartz[59]	1951	24	0	At six and one-half months		Died	--
Strauss and Tarachow[60]	1937	24	Not stated	Ninth month	Not stated	Lived	--
Stroink[61]	1936	33	iii	Immediately post partum	Spontaneous	Lived	--
Sullivan, et al.[62]	1953	23	0	Term	Cesarean section	Died	--
Trodella[63]	1952	23	0	Third day post partum	Low forceps	Lived	Fourth post-partum day
Walton[64]	1953	35	Not stated	Thirtieth week	Spontaneous	Lived	--
Present authors	1955	21	iii	Sixth month	Spontaneous	Lived	Sixth month
	1955	27	0	Eighth month	Undelivered	Died	--

TABLE III. AGES OF 79 PATIENTS IN WHOM RUPTURE OF CEREBRAL ANEURYSMS OCCURRED DURING PREGNANCY

AGE IN YEARS	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL
20-24	4	13	17
25-29	7	14	21
30-34	6	8	14
35-39	4	6	10
40-44	1	1	2
Not stated	10	5	15
Total	32	47	79

symptom is the onset of sudden severe headache which increases in intensity. This was noted in 59, or 74.7 per cent, of the cases where the symptoms were stated. This is sometimes accompanied by projectile vomiting. Depending upon the degree of hemorrhage, disturbances of sensorium occur, varying from drowsiness to loss of consciousness to coma. Coma occurred in 40, or 50.6 per cent, of these cases. In almost one-third of the cases there were generalized convulsions. Less commonly, visual or speech disturbances may be present, as well as varying degrees of paralysis.

Massive hemorrhage may result in sudden death in a previously normal individual. A common clinical finding is nuchal rigidity, frequently combined with a positive Kernig's sign. Papilledema is rarely encountered, although retinal hemorrhages are found more commonly. Less frequently, depending upon the size and site of the aneurysm, localizing signs may be present. Homonymous hemianopsia was present in 6 cases. Aneurysms of the middle cerebral artery usually give rise to olfactory or ocular motor nerve disturbances and may, in addition, exert pressure on the adjacent brain substance producing aphasia. Hemiplegia evolves from rupture of aneurysms located in the posterior fossa or rupture of the middle cerebral artery. Other cranial nerves may be incriminated but this was not demonstrated in this series (Table IV).

TABLE IV. SYMPTOMS AND FINDINGS IN 79 CASES OF RUPTURED CEREBRAL ANEURYSM DURING PREGNANCY

SYMPTOM OR FINDING	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL ANEURYSMS	PERCENTAGE OF CASES WHERE SYMPTOMS OR FINDINGS WERE STATED
Convulsion	9	16	25	31.6
Headache	21	38	59	74.7
Coma	19	21	40	50.6
Nuchal rigidity	16	24	40	50.6
Hemianopsia	4	2	6	7.6
Hemiplegia	1	3	4	5.1
Aphasia	0	2	2	2.5
None stated	9	4	13	

Blood pressure readings, prior to rupture, were available in 50 cases and confirmed hypertensive levels in only 5. Thus, complicating pre-eclampsia which may predispose to rupture was present in only 10.0 per cent of the cases. Following rupture, however, the blood pressure was elevated in 21 of the 49 cases wherein the pressure was recorded (Table V). The hypertension is cerebral in origin and is probably secondary to increased intracranial pressure. The actual incidence of hypertension following rupture may be greater than is noted herein, for shock with coma consequent to massive hemorrhage may mask the onset of hypertension. If these patients survive the initial episode, hypertension may later be manifested.

TABLE V. BLOOD PRESSURE ALTERATIONS IN 79 CASES OF CEREBRAL ANEURYSM DURING PREGNANCY RELATIVE TO RUPTURE

BLOOD PRESSURE	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL
Prior to Rupture.—			
Normal	12	33	45
Elevated	2	3	5
Not stated	18	11	29
Following Rupture.—			
Normal	11	17	28
Elevated	4	17	21
Not stated	17	13	30

Urinary findings were recorded in 39 cases, and albuminuria was found in 22. In 17 of these, albuminuria occurred for the first time following the subarachnoid hemorrhage (Table VI). This was a transitory finding and disappeared as the patient's condition improved. It probably results from irritation or increased pressure on the floor of the fourth ventricle, by a mechanism similar to that which produces glycosuria as demonstrated by Claude Bernard.[9] Another possible explanation for this phenomenon may be that it occurs through circulatory changes in the kidney, secondary to cerebral damage. A spinal tap will confirm the diagnosis of subarachnoid bleeding. The fluid was grossly bloody in 56 cases and was xanthochromic in 4 (Table VI). The fluid may be under increased pressure.

TABLE VI. URINARY AND CEREBROSPINAL FLUID FINDINGS IN 79 CASES OF RUPTURED CEREBRAL ANEURYSM DURING PREGNANCY

FINDINGS	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL
Albuminuria.—			
Present	5	17	22
Absent	8	9	17
Not stated	19	21	40
Spinal Fluid.—			
Bloody	23	33	56
Xanthochromic	0	4	4
Not done	1	2	3
Not stated	8	8	16

Incidence.—The incidence of rupture of cerebral aneurysms parallels the hemodynamic changes of pregnancy. Its occurrence is rare during the first trimester, and is greatest in the third, when the cardiac output and blood volume reach their peak. Thus 51.4 per cent of the cases wherein the time of rupture is known occurred near or at term (Table VII).

TABLE VII. TIME OF RUPTURE IN RELATION TO PERIOD OF GESTATION IN 79 CASES OF CEREBRAL ANEURYSM

TIME OF RUPTURE	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL
Ante partum.—			
First trimester	0	1	1
Second trimester	6	6	12
Third trimester	14	14	28
Not stated	2	0	2
In labor	1	9	10
Post partum.—			
First day	2	7	9
Second to fifth day	1	4	5
Sixth day or more	0	5	5
Not stated	2	0	2
Period of gestation not stated	4	1	5
Total			79

The fact that only 25.7 per cent ruptured during labor or within the first 24 hours post partum emphasizes the relatively minor role of stress in the causation of rupture during pregnancy. This finding does not differ materially from the ruptures in the nonpregnant state wherein 90 per cent occurred while the patients were at rest.

Differential Diagnosis.—Ruptured cerebral aneurysms must be differentiated from eclampsia and neurological conditions, such as cerebral venous

thrombosis, brain tumor, fulminating meningitis, or brain abscess. With the exception of meningeal angiomas, the other neurological complications rarely produce subarachnoid hemorrhage. Venous thrombosis is usually seen post partum, produces hemiplegia, and most commonly is associated with clear cerebrospinal fluid. When the fluid is bloody, angiography is indicated to differentiate the two.

Treatment.—The basic treatment for subarachnoid hemorrhage is medical, consisting of bed rest, sedation, and supportive therapy. Arteriograms, to localize the lesion, should be performed eight or more days after rupture. This may also disclose the presence of multiple aneurysms. Earlier angiography is reserved for patients whose condition demands emergency surgical intervention. After localization of the rupture, surgical correction is indicated. The surgical procedure selected depends upon location, type, and accessibility of the lesion. Intracranial ligation is reserved for narrow-necked pedunculated aneurysms. For other types of aneurysms originating from branches of the internal carotid artery, ligation of the internal or common carotid artery is indicated. Most aneurysms located in the posterior portion of the circle of Willis are inaccessible and not amenable to surgical correction.

Eleven patients in this series were treated by surgical means, 6 during the course of pregnancy. There were no maternal or fetal deaths in these cases. The results are encouraging and may indicate that successful surgery may be performed despite coexisting pregnancy, but a definitive opinion must await evaluation of a larger series.

Comment

The infrequency of the diagnosis of ruptured aneurysm is a reflection not only of the paucity of knowledge of the syndrome, but of its similarity to eclampsia, the more common obstetrical complication. As early as 1898, Lazard[29] stated that some cases treated as eclampsia were actually ruptured cerebral aneurysms. Despite half a century of obstetrical progress and repetition of this fact by others, ruptured aneurysms and other neurological complications of pregnancy have not received sufficient emphasis in the teaching of obstetrics. Since the majority of ruptures of aneurysms occur when eclampsia is the expected finding, it is readily understandable why the true diagnosis is overlooked. The circumstances and symptoms readily fit the diagnosis of eclampsia to everyone's satisfaction.

The differentiation of a ruptured cerebral aneurysm from eclampsia frequently may be impossible. In subarachnoid hemorrhage, history of a preexisting toxemia is usually lacking and the presumptive diagnosis of a cerebral aneurysm may be proved by angiography. Roentgenological studies are not infallible since aneurysms have been found at operation or postmortem examination which were not demonstrated by angiography. In addition, aneurysms of the posterior portion of the circle of Willis are not usually visualized by anterior or carotid angiography. These may be demonstrated by posterior or vertebral arteriograms. Because of dangers inherent in the procedure, however, and the surgical inaccessibility of the lesions, posterior angiography is not usually performed.

The presence of subarachnoid bleeding is readily confirmed by bloody spinal fluid obtained upon lumbar puncture. Although this is relatively a simple

procedure, it is amazing how infrequently it was performed even when warranted by the clinical findings. In many fatal cases the diagnosis of cerebral hemorrhage has never been confirmed by lumbar puncture or autopsy. The danger of sudden death secondary to this procedure has been greatly overemphasized. In fact, spinal tap was an essential component in the therapy of eclampsia until fairly recently.

Lumbar puncture usually confirms the presence of a subarachnoid hemorrhage. The cerebrospinal fluid is uniformly bloody under increased pressure, and does not clot upon standing. If the tap is performed four or more days after rupture, the fluid becomes xanthochromic and crenated or ghost cells may be demonstrated. Only too frequently a bloody cerebrospinal fluid is attributed to a traumatic tap and obscures the actual diagnosis. A simple procedure readily differentiates the two. On standing, the supernatant fluid of a traumatic tap is clear where that of hemorrhage is xanthochromic. The diagnosis of an aneurysm may be confirmed by cerebral angiography or occasionally by noting calcification within the sac wall on a routine skull x-ray.

The value of spinal tap in the pregnant patient suffering generalized seizures, unexplained coma, or severe headache with nuchal rigidity not following spinal anesthesia is that it not only will disclose the presence of subarachnoid hemorrhage, but also will influence subsequent treatment. Bloody spinal fluid strongly suggests the presence of an unsuspected ruptured aneurysm. However, extensive cerebral hemorrhage is found in 15 to 20 per cent of autopsied patients who die of eclampsia.[10] The primary lesion in these individuals is thought to be intracerebral bleeding with secondary perforation into the subarachnoid space. This information may influence the management of the eclamptic patient. In these cases, it may be advantageous to delay induction of labor or abdominal delivery for longer than the usual 24 hour period following stabilization of the convulsive state. Termination of pregnancy is indicated in the presence of progressive cerebral bleeding, only if the general condition of the patient is rapidly deteriorating.

In postpartum cases the differential diagnosis between cerebral vascular accidents and eclampsia is most important, for early ambulation is contraindicated in all cases of cerebral hemorrhage regardless of cause. In the absence of previous evidence of toxemia, postpartum eclampsia should not be diagnosed until neurological examination has ruled out cerebral vascular complications (such as ruptured aneurysm or venous thrombosis). It is possible that adequate neurological consultation and study would have shown many of the reported cases of postpartum eclampsia to be actually cerebral vascular accidents.

Despite the high incidence of massive cerebral hemorrhage reported, Dieckmann[10] feels that petechial rather than gross hemorrhages are the characteristic pathological finding in the brains of eclamptic patients. Since normal cerebral vessels can withstand pressures much higher than those encountered even in severe toxemia, it is apparent that vascular disruption occurs in already weakened vessels. Syphilitic and arteriosclerotic vascular changes

are not frequently found in these patients and arterial damage due to long-standing hypertension is common only in those with toxemia superimposed on chronic hypertension. In the majority, no vascular lesion was demonstrated; in fact, the source of the bleeding was not found. It is probable that hemorrhage originated from a rupture of a hypoplastic vessel or an aneurysm and the intracerebral bleeding was really secondary rather than primary. Many investigators noted that there was an inverse ratio between their interest in the problem and the frequency of subarachnoid hemorrhage of undetermined etiology. As a result, more careful dissection of the cerebral vascular tree was performed and revealed many aneurysms which would have been overlooked. Thus, Hamby,[24] in autopsy material, was able to demonstrate ruptured aneurysm in 91.4 per cent of cases of spontaneous subarachnoid hemorrhage. The application of this meticulous technique in eclamptic patients whose fatal outcome is attributed to cerebral vascular accidents may disclose rupture of an aneurysm as the source of hemorrhage. This was demonstrated by Richardson and Hyland[32] and Rhoads.[33]

The question to be answered is, Does pregnancy per se precipitate rupture of a cerebral aneurysm? It is apparent from this analysis that the hemodynamic changes of pregnancy rather than the stress of labor are the prime factor in the causation of aneurysm disruption. In this series, most of the ruptures occurred in the third trimester or at the peak of the cardiac load. It is difficult, however, to evaluate the full significance of this factor since all multiparas in this report withstood similar physiological changes and stress during previous gestations with no detrimental effect (Table VIII). Further doubt as to the significance of pregnancy as a cause of rupture arises when the large number of proved congenital cerebral aneurysms appearing in recent literature is considered. From the age group of women involved, it may be assumed that a large number were multiparas. In these women rupture occurred many years after their last delivery. In contrast to what one would anticipate, strain such as labor played a relatively minor role in precipitating arterial disruptions. Similar findings have been noted in the nonpregnant state. Magee[11] reported that in only 10 per cent of his cases was the accident associated with exertion.

TABLE VIII. PARITY IN 79 CASES OF RUPTURE OF CEREBRAL ANEURYSM DURING PREGNANCY

PARITY	PROVED ANEURYSM	PROBABLE ANEURYSM	TOTAL
Primiparas	11	23	34
Multiparas	9	17	26
Not stated	12	7	19
Total			79

In addition, the incidence of rupture in males of this age group is similar to that in females,[12] and if pregnancy were an important factor, there should be a significantly higher incidence in women.

The presence of coma was the only symptom of prognostic value and was usually indicative of a fatal outcome. Only 13, or 32.5 per cent, of the 40 patients in this series with coma survived. Seven of these had surgical intervention. Operation was not performed in any of the fatal cases.

The mortality rate of subarachnoid hemorrhage during pregnancy does not differ materially from that in the nongravid state. In this series, the mortality rate (maternal) was 46.7 per cent and compared favorably with the figure of 56.1 per cent derived from a pooled series of 835 cases reported in the literature.[11, 13, 14, 15] In the pooled series it was noted that 37.7 per cent died with the first attack and, of the survivors, 68.1 per cent succumbed with the second episode. This appears to indicate the advisability of surgical intervention following the initial hemorrhage.

Probably the most important problem confronting the obstetrician in these cases is to decide upon the mode of delivery and the advisability of future childbearing. Opinions in this regard vary, and the ideal method of delivery is still debatable.

One group contends that in all cases following rupture of a cerebral aneurysm elective cesarean section should be performed to obviate the strain of labor. Others, however, have utilized the vaginal route in pregnancies complicated by rupture of an aneurysm and in subsequent ones. From the limited data available, no definitive conclusion may be reached (Table IX). In cases of antepartum rupture, abdominal delivery did not appear to decrease the maternal mortality rate. Furthermore, abdominal delivery did not prevent the occurrence of the initial episode of cerebral hemorrhage during the puerperium. The final outcome in the few cases of subsequent pregnancies reported was similar regardless of the mode of delivery. As discussed earlier, however, the stress of labor is minor as compared with the hemodynamic changes in predisposing to rupture of an aneurysm. Therefore, it is difficult to visualize any advantage in the abdominal route since it does not eliminate the stress of increased circulatory dynamics. In cases further complicated by pre-existing hypertension or the development of toxemia, earlier termination by cesarean section is indicated.

TABLE IX. MODE OF DELIVERY IN 79 CASES OF CEREBRAL ANEURYSM

	PROVED ANEURYSM			PROBABLE ANEURYSM			
MODE OF DELIVERY	TOTAL CASES	LIVED	DIED	TOTAL CASES	LIVED	DIED	NOT STATED
Ante partum.—							
Vaginal	2	1	1	14	10	4	0
Abdominal	10	5	5	8	6	2	0
Undelivered	6	0	6	4	0	4	0
Not stated	5	2	3	4	1	0	3
Post partum.—							
Vaginal	3	3	0	13	10	3	0
Abdominal	0	0	0	2	2	0	0
Not stated	2	0	2	2	0	1	1
Time not stated.—							
Not stated	4	0	4	0	0	0	0
Grand total	32	11	21	47	29	14	4

Although no definitive policy may be formulated, future pregnancies are not contraindicated following surgical correction of the aneurysm. Because of the high mortality attendant upon rupture, all individuals with cerebral

aneurysms, unruptured or ruptured, should be advised to have surgical correction prior to pregnancy. However, when the ruptured aneurysm has been treated only medically or is inaccessible to surgery, the chances of a second episode of hemorrhage are present with or without a future pregnancy. Although the greater cardiac output and circulatory volume increase the hazard, uneventful pregnancies have been reported in these cases.

The decision in the medically treated cases in regard to future childbearing must be individualized, and any definitive opinion must await the accumulation and analysis of additional data.

Summary and Conclusions

1. An analysis of 79 cases of proved or probable cerebral aneurysm in pregnancy is presented. Two of these are reported for the first time.

2. These aneurysms are congenital in origin.

3. The incidence of rupture parallels the hemodynamic changes of pregnancy. The stress of labor plays a relatively minor role.

4. The symptoms commonly produced simulate those of eclampsia.

5. Spinal tap and angiography confirm the diagnosis.

6. Surgical ligation is indicated wherever feasible.

7. From this analysis abdominal delivery offers no advantage over the vaginal route except for obstetrical indications.

8. Pregnancy per se does not appear to increase the incidence of rupture of cerebral aneurysms or to increase the mortality rate.

9. The necessity of neurological consultation and study in "questionable" cases of eclampsia is stressed.

10. A stronger emphasis in obstetrical teaching will create an awareness of the problem and result in the correct diagnosis being made more commonly.

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PREMATURE RUPTURE OF THE MEMBRANES

A Clinical Study

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THERE is a paucity of information in the literature with regard to the clinical aspects of premature rupture of the membranes. A recent survey failed to disclose a single article in which all the following questions were answered. How soon after premature rupture of membranes will labor ensue? Should all such patients be hospitalized? Is amnionitis a likely sequela? Are antibiotics effective or necessary? Is presentation an etiological factor? This study was undertaken for the purpose of clarifying the natural course of events after premature rupture of the membranes and to ascertain the answers to these questions.

One hundred consecutive cases of premature rupture were studied over a period of eleven months. Cases were selected on the basis of rupture of the bag of waters at 37 weeks or less, based on the estimated date of confinement. During this study there were 2,481 deliveries, an incidence of premature rupture of 4 per cent.

TABLE I. LENGTH OF GESTATION

WEEKS	NO. OF PATIENTS
37	13
36	38
35	7
34	6
33	3
32	7
31	4
30	7
25-29	8
20-24	6
less than 20	1

Upon admission to the hospital, these patients were questioned as to the time rupture took place and when signs of labor began, and any prenatal complications were noted. They were then examined to determine if amniotic fluid was leaking or draining from the vagina and whether labor was in progress. All of these patients were admitted to the hospital immediately upon the notification of their obstetricians that rupture of the membranes had taken place. They were all kept on complete bed rest for varying lengths of time and were given antibiotics at the discretion of their obstetricians. In most instances, patients were discharged in 48 to 72 hours if labor had not begun. Patients who were placed on antibiotics on admission, for the most part were not continued on them after discharge.

Time of Rupture.—It is interesting to note that in 50 per cent of the patients studied rupture occurred at or about the thirty-sixth to thirty-seventh week of gestation and that in 75 per cent of the patients rupture occurred after the thirty-second week. There were only 3 cases in which a history of premature rupture of the bag of waters in a previous pregnancy could be elicited. Seventy-nine patients in this series were multigravidas and 21 were primigravidas.

Etiology.—No apparent etiological factor became evident after these cases were reviewed. There were no cases of hydramnios and trauma was not indicated in any instance. There were only 16 cases in which any significant prenatal complication or previous medical condition was noted.

TABLE II. PRENATAL COMPLICATIONS

COMPLICATION	NO. OF CASES
Spotting	3
Severe anemia	2
Pre-eclampsia	4
Pyelitis	1
Treated syphilis	1
Multiple premature births	1
Hypertension	2
Healed tuberculosis	2

There were 62 Negro and 38 white patients in the study. There were 82 vertex presentations, 12 breech presentations, and 6 patients underwent cesarean section. Prolapse of the umbilical cord occurred in 2 cases, only 1 of which was a breech presentation. The 6 patients who underwent cesarean section did so because of the following indications: repeat section, 3; transverse lie, 1; placenta previa, 1; previous myomectomy, 1.

The patients ranged in age from 15 to 40 years. The greatest incidence occurred between the ages of 25 and 29 years.

TABLE III. AGE

YEARS	NO. OF PATIENTS
35-40	8
30-34	25
25-29	36
20-24	23
15-19	8

Antibiotics.—A total of 39 patients received antibiotics (penicillin, streptomycin, Gantrisin) either alone or in combination. Penicillin alone was given to 31 patients in a dosage of 300,000 units intramuscularly, twice daily. Five patients received penicillin and streptomycin (0.5 Gm. twice daily) and 3 patients received Gantrisin (0.5 Gm. four times daily). Antibiotics were given primarily while the patients were hospitalized. Clinic patients were given Gantrisin upon discharge from the hospital if undelivered.

Of the 100 cases studied there were 2 cases of amnionitis. Both of these occurred in patients who had received antibiotics. No etiological factor was discovered in either of these cases.

Induction.—Either intramuscular or intravenous Pitocin was given in 11 cases in an attempt to induce labor. The majority of these patients were considered to have large enough babies, or in several cases a dead baby was suspected. Induction was attempted in spite of possible amnionitis. No difficulties were encountered through the use of Pitocin and induction was successful in all cases.

Onset of Labor.—A point of major interest in this study was to determine the answer to the question—what is the time relationship between the premature rupture of the bag of waters and the onset of labor? Fifty-eight patients noted the onset of labor within 24 hours following the rupture of the membranes. Twenty-three of this group noted the onset of labor either simultaneously or within one hour of rupture. Table IV gives a more detailed study of the time relationships.

TABLE IV. ONSET OF LABOR FOLLOWING RUPTURE OF MEMBRANES

TIME	NO. CASES
0-1 hour	23
1-6 hours	5
6-12 hours	15
12-24 hours	15
24-36 hours	11
48 hours or more	31

Time of Delivery.—Sixty-nine patients were delivered within 48 hours after rupture of the membranes and 79 were delivered within 72 hours. The longest interval in this series occurred in a 25-year-old Negro patient, para i, gravida iii, in whom rupture occurred at the end of the twelfth week* and who was delivered at the end of the thirty-sixth week. This patient was given Gantrisin (0.5 Gm. four times daily) for approximately a two-week period, during which time she continued to lose amniotic fluid daily. The medication was discontinued when the daily leakage stopped.

TABLE V. DELIVERY FOLLOWING RUPTURE OF MEMBRANES

TIME INTERVAL	NO. DELIVERED
6 hours or less	8
6-12 hours	17
12-24 hours	23
24-48 hours	21
48-72 hours	10
72-96 hours	3
4-7 days	8
7-14 days	4
14-28 days	2
more than 28 days	4

Summary

1. One hundred cases of premature rupture of the membranes at 37 weeks' gestation or less were studied from a total of 2,481 admissions, with an incidence of 4 per cent.

2. Patients with rupture of the membranes were placed on complete bed rest for 48 to 72 hours and discharged if not in labor and if, in the majority of instances, loss of amniotic fluid had completely stopped. Antibiotics were given to 39 patients. Amnionitis developed in only 2 cases, in both of which antibiotics had been given.

*When this patient was admitted at the end of the twelfth week, the diagnosis of ruptured membranes was made on the basis of the history as given by the patient, together with a positive nitrazine paper test and the objective evidence of the loss of amniotic fluid. When she returned at the end of the thirty-sixth week in active labor, the membranes were considered to be ruptured as there was no additional indication during labor or delivery that the membranes were intact.

3. Fifty per cent of the patients studied were admitted at about the thirty-sixth to thirty-seventh week of gestation. Only 25 per cent of the total number of patients studied had ruptured membranes prior to the thirty-second week.

4. No etiological factor was apparent, nor did age, race, or presentation appear to influence premature rupture of the membranes.

5. In 79 per cent of the patients labor began and delivery occurred within the first 72 hours after rupture.

6. There were 2 cases of prolapse of the umbilical cord, a higher incidence than is usually seen.

Conclusions

It may be concluded that labor and delivery will most likely occur within the first 72 hours after rupture of the membranes. Hospitalization after this period is probably not justifiable unless there are other indications.

From these clinical observations it appears that all patients with ruptured membranes should be hospitalized and observed for at least 72 hours. If labor does not ensue after this interval and in the absence of further leakage of amniotic fluid, it is probably safe to say that labor will be delayed for some time depending upon the length of gestation. It is apparent from this study that antibiotics did not play a satisfactory role in the prevention of amnionitis. It is probably equally important to instruct patients in proper perineal hygiene for the prevention of infection. Prolapse of the umbilical cord is more likely to occur with premature rupture of membranes.

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THE MANAGEMENT OF THE NEAR-TERM PREGNANT PATIENT WHO DIES UNDELIVERED

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THE opportunity of delivering a living infant from a recently deceased mother is a rare privilege. Most physicians will never experience this satisfaction in their entire lifetime of medical practice. Therefore, when the situation presents itself, it is imperative that the proper measures be instituted promptly and efficiently if favorable results are to be anticipated.

In a survey of the obstetrical records at the Akron City Hospital from the years 1946 through 1955, 9 undelivered mothers died during the last trimester of gestation. In the same ten-year period there were 45,000 live babies born. This is an incidence of 0.02 per cent or 1 in 5,000 live births. Of these 9 mothers, only 5 were delivered posthumously (one vaginally and 4 by cesarean section). We have 2 living children whose photographs appear in the case reports later in the article (Figs. 1 and 2). This is a salvage rate of 40 per cent of the 5 babies delivered, or 22 per cent of the infants of the 9 mothers who died undelivered. A brief summary of the 9 cases will be submitted, as well as a review of the current literature pertaining to this subject. We will also present several precautionary measures which have been adopted at our hospital whereby some of the preventable errors in the management of this situation may be avoided.

The 4 cases in which delivery was not accomplished will be considered very briefly at the onset. In 2 of these 4, fetal death was evident hours before the death of the mother. Obviously, delivery in these 2 cases was not indicated. Both mothers were very young primigravidas.

CASE 1.—The patient was 15 years old, with a long history of nephritis. She died in an acute exacerbation of kidney disease with superimposed eclampsia, at thirty-two weeks' gestation. This patient experienced two convulsions at home and one en route to the hospital. Her condition never became satisfactory for delivery. The fetal heart tones disappeared six hours after admission and the mother died six hours later.

CASE 2.—A 17-year-old primigravida at thirty-six weeks' gestation was admitted in a comatose condition and in respiratory embarrassment. No fetal heart tones were heard at any time following admission. She died six hours later of extensive bronchopneumonia. The membranes were ruptured artificially and intravenous Pitocin was given but the attempt at delivery was unsuccessful.

In the remaining 2 patients who were not delivered, we admit guilt by the "sin of omission."

CASE 3.—A 25-year-old gravida iii, para ii, cardiac patient with a history of rheumatic heart disease was hospitalized forty-eight hours prior to her death. The fetal heart tones were audible on each examination. Postmortem studies showed the cause of death to be

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acute passive congestion of the lungs, liver, and spleen. The pathologist also reported a normal male fetus of approximately thirty weeks' gestation in utero. No attempt had been made to salvage the baby.

CASE 4.—The other patient presents a similar tragedy. A 28-year-old gravida iv, para ii, eclamptic patient, she was in the hospital twenty-four hours before she died of a cerebrovascular accident. She was in the eighth month of gestation. The history obtained included the delivery of a stillborn fetus two years previously at which time she had experienced an episode of high blood pressure and albuminuria. No records were made of fetal heart tone examinations on the present admission. Posthumous delivery was not attempted and no autopsy was performed. The highest recorded blood pressure was 210/130.

The only redeeming feature for our department is the fact that not one of the obstetrical attending staff was consulted, nor was the obstetrical house staff notified of admission or death of either of these two patients for they were admitted outside of the obstetrical division.

CASE 5.—Our fifth case is that of a patient who was admitted directly to the delivery floor and ready for delivery. She was immediately anesthetized with open-drop ether by the intern on the floor. No history had been obtained. Death occurred twenty minutes after anesthesia was begun, the cause being a combination of aspiration of vomitus and shock due to severe vaginal hemorrhage. The chest was opened but cardiac massage was of no benefit. A term baby was delivered by low forceps about ten minutes after the patient stopped breathing. There were no fetal heart sounds at birth and no attempts were made at respiration. The baby was considered stillborn.

In the remaining 4 cases cesarean sections were performed. The first 2 to be summarized are those in which the babies failed to survive.

CASE 6.—A 26-year-old gravida ii, para 0, at thirty-four weeks' gestation, was admitted with a history of healed pulmonary tuberculosis. Her complaint on entrance was of an upper respiratory infection of one week's duration and hemoptysis of about 1 pint of blood on the day of admission. Fetal heart tones were heard and the uterus was the size of a near-term gestation. She died two hours after admission of a sudden recurrence of the pulmonary hemorrhage. The fetal heart tones were checked and present. Some delay occurred in an attempt to obtain permission for operation from the husband. Twelve minutes after the mother's death, a 6 pound baby was delivered alive. However, after forty minutes the baby died. Cardiac sounds were present for this length of time, but spontaneous respirations were never established.

CASE 7.—We also lost the baby in the seventh case. A 22-year-old Negro woman, gravida i, para 0, at thirty-six weeks' gestation, was admitted twenty-four hours before her death. She was admitted in a semicomatose state. She was confused and disoriented. Her previous complaints were severe headaches, fever, and dizziness. On admission the blood pressure was normal, fetal heart tones were present, and the uterus was the size of a term gestation. She became progressively worse and died very suddenly about twenty-four hours later. A lumbar puncture and spinal fluid examination was performed after several previous unsuccessful attempts. A neurological consultant believed the cause of death to be a brain abscess. A classical section eight minutes after the death of the mother produced a 6 pound baby boy who also had cardiac sounds for several minutes after birth but attempts at establishing respirations failed.

We are very happy to report the last 2 cases. To be able to report 2 successful postmortem cesarean sections places our institution in a rather unique position. Case 8 has previously been reported much more completely by the operator.[1] A brief summary of his article follows.

CASE 8.—The patient was a 42-year-old gravida iv, para iii, at twenty-nine to thirty weeks' gestation, admitted in acute distress with pale, cold, and clammy skin. Fetal heart tones were present and the uterus was about seven months' size. Seven hours after admission she became much more dyspneic, cyanotic, pulseless, and died in circulatory collapse. The cause of death established at autopsy was a ruptured dissecting aneurysm of the aortic arch. Seven minutes after she died a 3 pound baby girl was delivered by classical section. The baby gasped but no immediate respiratory attempts followed. Oxygen was given by tracheal catheter and six minutes later spontaneous respirations were established. The girl is now 3 years old (Fig. 1).

Fig. 1.

Fig. 2.

Fig. 1.—Baby delivered in Case 8. Child 3 years old at time photograph was taken, October, 1955.

Fig. 2.—Baby delivered in Case 9. Child 1 year old at time photograph was taken, October, 1955.

CASE 9.—The patient had been under the care of the surgical staff for treatment of what appeared to be idiopathic thrombocytopenic purpura. At the time of her final admission she had extensive ecchymotic areas covering her body. She was 31 years old, a gravida ii, para i, white woman at approximately thirty weeks' gestation. Since the third month of pregnancy she had developed progressively more and more subcutaneous hemorrhages and her general condition had markedly deteriorated. The disease had advanced to the point where a splenectomy seemed to be the only possible chance for survival of the patient. She was given Levophed and had been on cortisone in an attempt to bolster her condition to a point where operation could be considered. A combined thoracoabdominal approach was chosen for the splenectomy. Cardiac aystole ensued and massage was instituted immediately and continued for fifteen minutes with unsatisfactory response. The junior author was invited to deliver the baby. Fetal heart tones were checked and were audible. A 4 pound baby boy was delivered rapidly by classical cesarean section. The heart rate at birth was 40 per minute. Mouth-to-mouth respirations were immediately

begun. The fetal heartbeat improved steadily. Oxygenation was maintained by mouth-to-mouth breathing for about forty minutes before satisfactory spontaneous respirations were established. The infant was discharged on the twenty-fifth hospital day weighing 5 pounds, 3 ounces, and in good condition. The photograph, Fig. 2, was taken several months ago when the boy was 1 year of age. Growth and development have been entirely normal. At operation the mother was found to have a large carcinoma of the stomach with grapefruit-sized bilateral Krukenberg tumors of the ovaries.

There is a paucity of recent literature on this subject. We have referred to one article and would like to use some material from two additional excellent publications.

Dr. Mary Helmer[2] stated that only 80 postmortem cesarean sections had been reported in her country. She dealt mainly with the causes of maternal death in the cases in which the operation had been performed. In the order of decreasing frequency she listed: (1) pulmonary tuberculosis, (2) toxemia, (3) ruptured aneurysms, (4) cerebrovascular accidents, (5) pneumonia, (6) cardiac decompensation, and (7) poliomyelitis.

We would also like to recommend Dr. Henry P. Lattuada's[3] article in which he reviewed the recent literature as well as the entire history of this operation. Regarding the incidence, he stated that only 22 successful cases were reported in the world literature from 1937 to 1950 and only 10 of these occurred in our country. He agreed that only a very few physicians are ever offered the opportunity to perform a postmortem cesarean section and obtain a living infant.

In the same article, he answered many questions regarding the legal aspects involved in this emergency situation. His conclusions included the following: (1) The courts will uphold a physician for performing the operation. (2) It is not certain what crime, if any, is committed when a physician fails to do the operation, and it is an open question whether the father's refusal to consent to the operation would protect the physician in event of court trial in such an instance. (3) An unborn viable child is capable of independent existence and should be regarded as a separate entity.

Conclusions

From the survey which we have completed and submitted, we believe that any gestation which has progressed beyond the twenty-eighth week has produced a potential independent human life and in the case of the death of its host should be given every possible chance of survival. We further believe that every minute of time lost after the death of the mother decreases the chances of satisfactory rewards for the efforts extended. Twenty minutes is about as long as one can expect life to persist in utero after the mother's death. There is no authentic record of survival of the infant when more than twenty-five minutes have elapsed between the mother's death and the infant's delivery. Resuscitation problems are many times greater if the time interval exceeds five minutes. The more sudden the death of the mother the better the chances of fetal salvage. A physician is never justified in searching long after a patient's death for signs of fetal life. If positive signs of fetal life were present shortly before the death of the mother, we must assume the fetus is alive and immediately deliver the baby. Legally, we are not justified in delaying for the purpose of obtaining operative permits.

With these convictions clearly demonstrated by our study, we have made an effort to obviate some of the errors previously committed.

1. The admitting clerks are instructed to inform the chief obstetrical resident immediately upon the admission of any pregnant patient who is beyond the twenty-eighth week and is to be admitted to any room outside of the labor and delivery section of the entire hospital.

2. Upon notification of such admission, the house officer will familiarize himself with the patient and her attending physician immediately.

3. The nurses and all floor personnel in charge of the patient are advised to follow the patient and her pregnancy very closely and to notify the senior obstetrical resident on duty, at once, if the condition of the patient becomes critical.

4. Depending upon the seriousness of the patient's illness, an emergency cesarean section tray is kept available on the floor and the obstetrical house officer remains in immediate attendance.

By observance of these principles we have been able to keep all personnel attending the patient alert to the possibility of saving the life of a viable infant in the event of the death of the mother.

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"MENOURIA" FOLLOWING LOWER SEGMENT CESAREAN SECTION

A Syndrome

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THE object of this paper is to draw attention to an interesting syndrome which may rarely follow lower segment cesarean section and to provide an explanation for its peculiar signs and symptoms. A vesicocervical fistula with incontinence of urine occasionally occurs as a complication of this operation. This is not different from vesicocervical fistulas which may complicate other types of difficult labor or gynecological operations and the literature is full of references to this condition and of descriptions of different operative procedures designed for its treatment.

Very rarely, however, a different type of bladder fistula may complicate lower segment section which is, curiously enough, characterized by the complete absence of urinary incontinence. The patient, instead, presents herself some time after the operation complaining of amenorrhea and of cyclic voiding of blood-stained urine at the expected time of her periods. Examination discloses that a vesicouterine fistula is present and that although no urinary leakage takes place and not a drop of menstrual blood passes through the natural passages, the cervical canal is perfectly patent.

Careful search of the literature has shown that only 6 such cases have so far been reported and that no reference to this clinical entity is to be found in any of the standard works on gynecology or urology except for a statement by Herbut[7] in the first volume of his *Urological Pathology* that in some cases of uterovesical fistula "the patient may void blood during the menstrual period or menstruation may be entirely by the way of the bladder." It is perhaps because of the rarity of the condition and the fact that it is not even mentioned in most of the gynecological and urological texts that few clinicians are aware of its occurrence and that no logical explanation has been put forward to account for its curious manifestations.

The 6 previous cases were reported by Laffont and Ezes,[9] Ingelman-Sundberg,[8] Musset and Mazingarbe[11] who contributed two cases, Stening,[15] and Falk and Tancer.[5] All cases have shown the same typical features, namely, the presence of a vesicouterine fistula, patency of the cervical canal, absence of urinary incontinence, absence of vaginal bleeding, and vesical menstruation. We have coined the name "menouria" to describe the latter feature which invariably constitutes the most important presenting sign. All cases have occurred after an abdominal lower segment cesarean section with the exception of Ingelman-Sundberg's case which followed a vaginal lower segment operation with the delivery of a 24 cm. long fetus. A unique case was reported by Burr[4] in which the same clinical features followed the induction of abortion by a catheter which had been left in the uterus and sloughed into

the bladder. The patient had in addition symptoms of severe bladder irritation for which a suprapubic cystotomy was performed and the catheter removed from the bladder but the fistula was not closed. Urinary sepsis subsided but the entire menstrual flow continued to pass through the bladder. No urinary incontinence was present and the patient refused further operative treatment since she "felt more fortunate that the menstrual flow is being taken care of in what she considers a more sanitary and convenient manner than formerly."

Last year we came across a case which in no way differed from the 7 cases previously described in the literature. At the time we were engaged in investigating the sphincteric mechanism of the bladder by sphincterometrography and air sphincterometry and our attention had been drawn to the possible presence of a sphincteric mechanism at the uterine isthmus by the work of Palmer,[13] Westman,[17] and others, and we were in fact beginning to undertake the operation of isthmorrhaphy for habitual abortion due to cervical incompetence on the lines we had witnessed in Palmer's clinic in Paris. It therefore seemed to us possible that the absence of urinary leakage through the cervix and the fact that the menstrual blood passed through the fistulous tract into the bladder and not via the natural passages might be due to the sphincteric action at the isthmus uteri. The case was thoroughly investigated with this possibility in mind and the details of the previously reported cases were meticulously studied. The conclusion was reached that our theory was correct and that it indeed provides the only satisfactory explanation for the unique clinical features of this rare syndrome.

Case Report

Patient S. H. A. (Hosp. No. K 4470/55) was admitted to the gynecological section, Kasr-el-Aini Hospital, Cairo, on March 31, 1955. She complained of sterility, of amenorrhea since her last delivery, and of cyclic hematuria occurring regularly at 30 day intervals and lasting for 4 to 5 days. There was absolutely no pain or other urinary symptom, the patient was perfectly continent, and there was no vaginal bleeding or discharge. The patient had had 2 normal labors but her last delivery, 2½ years before admission, was by lower segment section performed in another hospital for severe antepartum hemorrhage. An almost full-term stillborn baby was delivered and the patient made an uneventful recovery and was discharged after 2 weeks in perfectly good condition. Two months later, she noticed that her urine contained frank blood and blood clots and this condition lasted for 4 days. This gross hematuria subsequently occurred regularly at monthly intervals and the patient was annoyed, for she was having no periods although she never lactated, and suspected that her menstrual flow had mysteriously been finding its way to her urine for which condition she blamed the cesarean operation. The last episode of hematuria had terminated 5 days before admission.

On examination her general condition was fairly good. There was a nicely healed scar of a midline subumbilical incision extending from the upper border of the pubic symphysis to a point 2 inches below the umbilicus. The uterus was normal in size, moderately retroverted, and seemed to be somewhat adherent to the region of the bladder but there were no tenderness and no abnormality of the bladder or genital system. The urethral meatus was normal and when the patient was asked to cough or strain with the bladder moderately full no urine was seen to escape from the urethral meatus or from the cervix. The methylene blue test was performed by Resident A. Faris on April 2, and the result was reported as negative, i.e., the dye injected into the bladder failed to pass into the vagina or cervix.

Being completely unaware of the previous case reports, we suspected that a vesicouterine fistula probably was present as a result of the cesarean section and that the lower

segment or cervix had somehow been obliterated in the course of the operation. It was decided to pass a uterine sound through the cervix to demonstrate the site of the occlusion but to our great surprise the sound passed with great ease into the uterine cavity. (n.b., Laffont and Ezes who reported the first case also expressed after a negative methylene blue test "their great surprise that it was with the greatest facility that one could penetrate into the uterine cavity.") At that time, however, we had never heard of Laffont and Ezes' case and we began to doubt the correctness of our initial diagnosis. Cystoscopy was performed and showed an irregular depression about 1 cm. in diameter in the region

Fig. 1.

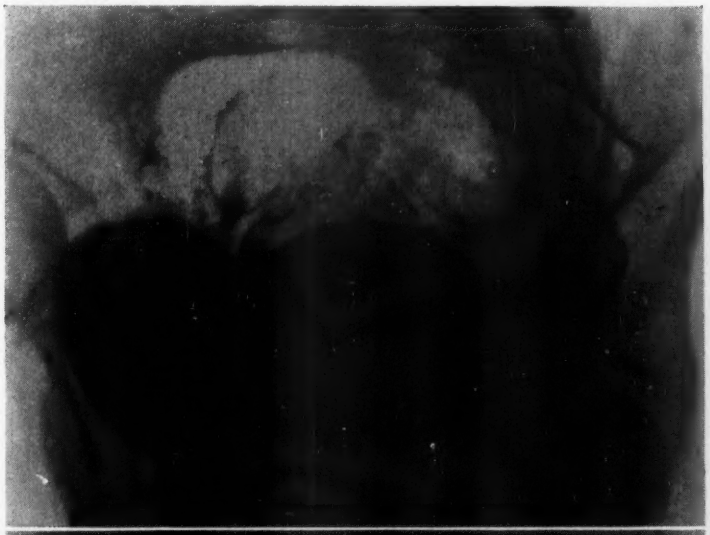

Fig. 2.

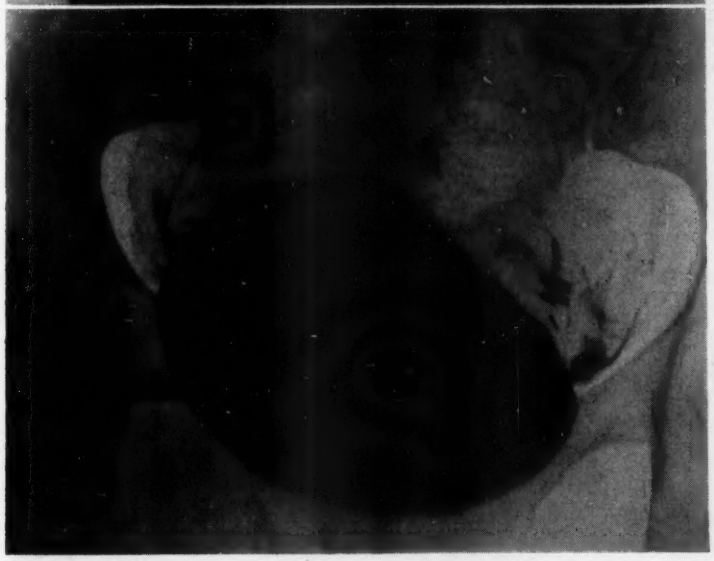

Fig. 1.—Oblique radiograph taken after injection of 10 per cent sodium iodide solution into the bladder. The radiopaque solution has passed through the fistulous tract and filled the cavity of the retroverted uterus.

Fig. 2.—Anteroposterior radiograph showing that the sodium iodide solution injected into the bladder has passed through the Fallopian tubes into the peritoneal cavity.

of the interureteric bar midway between the two ureteric orifices; the bladder was otherwise normal. The methylene blue test was then repeated by the author on April 7. The bladder was filled with the colored solution until the patient had a strong desire to void. No leakage occurred from the cervix. Strong pressure was then applied to the suprapubic region upon which the methylene blue solution was seen to escape from the cervical os. This established the presence of a fistulous communication between the bladder and the uterus. The fact that leakage occurred only when strong pressure was applied to the full bladder suggested that a certain resistance was present which could be overcome when the intravesical pressure was abnormally increased. Since the cervical canal was patent it occurred to us that this resistance might be due to the sphincteric action present in the region of the uterine isthmus.

On April 23 the urine was seen to contain frank blood and the hematuria lasted for 5 days but no pain or other urinary symptoms were present.

Cystography performed on May 5 by injection of 200 ml. of 10 per cent sodium iodide solution into the bladder showed that the uterine cavity was also filled by the radiopaque solution but no leakage occurred through the cervix (Fig. 1). A radiograph made immediately after pressure was applied to the suprapubic region showed that the radiopaque solution had then passed through the cervical canal and through the Fallopian tubes into the peritoneal cavity, showing that the pressure was sufficient to overcome the resistance of the isthmic and the tubal sphincters (Fig. 2). A study of Fig. 1 will show the interesting appearance of the junction between the uterine cavity and the cervical canal at the site of the supposed sphincter.

Pyelography showed the normal appearance of both kidneys. The blood urea was 22 mg. per cent and the renal function tests were normal.

The diagnosis of vesicouterine fistula having been established, it was decided to close the fistula by the abdominal transperitoneal route. This approach was chosen owing to the high position of the fistula above the level of the uterine isthmus and because it would allow for testing the validity of the isthmic sphincter theory by means of abdominal intrauterine insufflation on the lines previously described by Westman.

Operation.—(A. F. Y. assisted by Resident A. Faris, May 15, 1955.) Under spinal anesthesia the abdomen was opened by a midline subumbilical incision with excision of the scar of the previous operation. The uterus was pulled up into the wound and it was found that the bladder was adherent to the lower part of its anterior surface. A fine lumbar puncture needle connected by a sterile piece of rubber tubing to an insufflation apparatus and manometer was introduced through the fundus into the uterine cavity. Firm pressure was applied to the Fallopian tube close to the uterine cornu on either side to prevent passage of air through the tubes. The uterine cavity was then insufflated with air and it was found that the pressure recorded by the manometer rose only to 10 mm. of mercury and then fell down. The cervix was then clamped from below by means of a strong curved clamp and the insufflation repeated but the result was not different. It was noticed that air passed into the bladder.

The loose peritoneum of the vesicouterine pouch could not be defined owing to the presence of adhesions. With curved scissors the peritoneum on the anterior surface of the uterus was divided 1 cm. above the attachment of the bladder and by sharp dissection the vesicouterine space was entered and the bladder dissected downward. This dissection was not easy and some oozing took place, which was controlled. The fistulous tract between the uterus and the bladder was exposed and divided and the bladder pushed well down, exposing the vaginal cervix and the upper 1 inch of the anterior vaginal wall. The opening in the uterus was found to be rounded in shape and a little less than 1 cm. in diameter. The opening in the bladder was irregular and about 1.5 cm. in length and 1 cm. in breadth. Both openings were surrounded by dense scar tissue which was excised. The opening in

the bladder was closed transversely by two layers of interrupted sutures of No. 0 nonchromicized catgut, avoiding the bladder mucosa. The opening in the uterus was subsequently closed vertically by two layers of interrupted sutures of No. 1 chromicized catgut and avoiding the uterine mucosa. A free omental graft was then sutured to the anterior surface of the uterus to intervene between the closed uterine and vesical openings.

Insufflation was repeated with both Fallopian tubes closed as before and it was found that the pressure recorded by the manometer now rose to 85 mm. of mercury before

Fig. 3.—Sodium iodide cystography after the fistula had been closed and the patient became pregnant. Normal appearance.

Fig. 4.—Sodium iodide cystography after delivery (oblique view). The bladder appears normal and no leakage into the uterine cavity is seen.

it began to fall as the gas was heard to leak through the cervix. When the cervix was clamped and insufflation again performed the pressure rose to the maximal limit of 300 mm. of mercury and did not drop until the clamp on the cervix was released.

The vesicouterine peritoneum was sutured and the abdomen closed in layers. A self-retaining catheter was kept in the bladder for 10 days. Except for a slight rise of temperature on the first 4 postoperative days the recovery was uneventful.

Fourteen days after the operation the patient had a normal period which lasted 4 days. The entire menstrual flow passed per vaginam and the urine was quite clear. She was kept in the hospital until she had another absolutely normal period lasting from June 30 to July 2, and was discharged cured on July 11, 1955.

Follow-up.—The patient was requested in writing to come for re-examination and she was readmitted on April 16, 1956. She said that she had two entirely normal vaginal periods after discharge without a drop of blood passing in the urine. Subsequently her periods ceased but there was no hematuria and she found out that she had become pregnant. Her last period was about the middle of August, 1955. She did not at any time have urinary incontinence or any other urinary symptoms.

On examination it was found that she had a normal pregnancy of about 36 weeks' duration, the presentation was cephalic, and the back was anterior and to the left. Examination of the vagina, cervix, bladder, and urethra disclosed no abnormality. Cystography showed normal findings (Fig. 3) and on cystoscopy no abnormality was detected.

On April 21, 1956, she went into premature labor and had a normal spontaneous delivery of a healthy male child who weighed 6¼ pounds.

Cystoscopy performed again on April 30 showed the normal appearance of the postpartum bladder. The methylene blue test on May 2 was negative and cystography, also on May 2, showed normal findings (Fig. 4).

Both mother and child did very well post partum and were discharged on May 6, 1956.

Comment

Although the possible presence of a sphincter at the isthmus uteri was discussed by Stieve[16] and Schroder[14] among other earlier authors, the question has not received due attention until relatively recently. Westman[17] and Fuchs and Westman[6] concluded from their abdominal intrauterine insufflation studies that there is a functional sphincter at the junction of the cervix and corpus uteri, that this sphincter contracts rhythmically and that its contractions are probably independent of nervous control. Palmer[13] has shown by means of manometric hysterography that a sphincter is present at the uterine isthmus and that its abnormal relaxation may play a role in the etiology of habitual abortion. Borell and Fernström,[2] using an ingenious radiographic technique, also demonstrated that a functional sphincter, apparently under hormonal influence, controls the width of the isthmus uteri.

The syndrome described in this paper, which may follow lower segment cesarean section in the rare event when a vesicouterine fistula above the anatomical internal os complicates the operation, can be satisfactorily explained only by assuming that a sphincter is present at the uterine isthmus which prevents the passage of urine or menstrual blood through the patent cervix. It is probable that in normal menstruation the blood to some extent distends the uterine cavity and this is followed by relaxation of the sphincter with the rhythmic discharge of the menstrual flow. When a fistula is present above the internal os, the blood passes through the fistulous opening into the bladder, no distention of the uterus takes place, and the sphincter fails to relax. It may be interesting to review the etiology of spasmodic (primary) dysmenorrhea and the improvement or cure of this condition which commonly follows dilatation of the cervix, abortion, or labor in the light of this theory.

When a vesicocervical fistula is present below the level of the isthmus, the usual picture of complete urinary incontinence occurs and the menstrual flow passes through the cervix and not through the fistula into the bladder.

Some direct evidence was obtained in our case which lends support to the isthmic sphincter theory. When methylene blue or sodium iodide was injected into the bladder no leakage occurred through the cervical os, but when the bladder was filled with the solution and strong pressure was applied to the suprapubic region the solution escaped through the cervix. This can be explained by assuming that the resistance of the isthmic sphincter was overcome when the pressure to which it was subjected was markedly increased. It is interesting that when the patient coughed or strained, however, no such leakage occurred. This is probably because the uterine wall is thick and strong and prevents the transmission of increase in the intra-abdominal pressure to the inside of the uterine cavity.

Abdominal intrauterine insufflation before and after closure of the fistula also provided interesting information. Westman found, using the same technique in a normal case, that the pressure sufficient to overcome the resistance of the isthmic sphincter was 98 mm. of mercury. He mentioned that this pressure might vary from case to case but was never less than 25 to 30 mm. of mercury. In our case, before the fistula was closed, the pressure hardly rose to 10 mm. of mercury, showing that the gas passed through the fistula rather than through the sphincter. After closure of the fistula the manometric pressure rose to 85 mm. of mercury before the gas leaked through the cervix, which confirmed the conclusion of Westman that a functional sphincter exists in the region of the uterine isthmus.

Although cases showing the same typical features as our own have previously been reported, no explanation of their occurrence has hitherto been logically established. Laffont and Ezes who reported the first case conjectured that a valve mechanism of some sort might exist, while Falk and Tancer who reported the last one said that no such mechanism could be demonstrated. They did not attempt to account for the curious clinical findings but merely stated, "It is of interest to speculate on the reasons why urine does not flow from the bladder through the fistulous tract and hence out of the patent cervix. One must wonder, too, why the menstrual discharge flows through the bladder but not through a patent cervical canal."

The lower segment cesarean section has almost universally superseded the classical operation only in the last 20 years. This is perhaps why the first case of "menouria" following cesarean section was reported as late as 1947. It is interesting to consider the reasons why this syndrome appears to be so rare. The lower uterine segment is formed both from the isthmus and the part of the body of the uterus corresponding to the area of loose attachment of peritoneum.[3] The isthmus of the uterus is the part of the cervix between the histological internal os and the anatomical internal os. The upper limit of the bladder contact with the cervix is variable but it never reaches higher than the histological internal os.[3] For the syndrome to occur, the uterine fistula must be present in the part of the uterus above the level of the isthmus and its sphincter, i.e., it must have involved the upper part of the lower segment which is not related to the bladder. It is unusual to make the uterine incision so high in the lower segment, but should it be so placed the bladder will not have to be dissected downward to any considerable extent and it is very unlikely to be injured. If the incision is, as it should be, placed as low down in the lower segment as is practicable, the bladder must be dissected considerably downward and is therefore more liable to injury. It is for this

reason that vesicocervical or vesicocervicovaginal fistulas following the lower segment operation occur much less rarely than vesicouterine fistulas situated above the uterine isthmus.

The syndrome we have described in this paper presents very characteristic clinical features but because it is so rare and so ill recognized it is possible that it may have been mistaken for the less uncommon condition of endometriosis of the bladder. This may also occur after lower segment section and may cause cyclic hematuria. In endometriosis of the bladder, however, there will be normal vaginal periods, and the typical symptoms of pressure or discomfort in the vesicovaginal region, dysuria, frequency and urgency are usually but not always present.[12] The cystoscopy appearance is sometimes typical but cystoscopy alone will not always establish the diagnosis.[10] Antoine[1] noted a marked increase in the incidence of endometriosis of the bladder in Austria following the war when many vaginal hysterotomies were being performed to terminate pregnancy. One may wonder if some of these cases were not in fact unrecognized instances of the syndrome of "menouria." It appears advisable in all cases in which the possibility of vesical endometriosis after cesarean section or hysterotomy is suspected because of the presence of cyclic hematuria to perform cystography and hysterography in order to exclude the presence of a vesicouterine fistula, especially if other symptoms of endometriosis are lacking or if the cystoscopic appearances are not typical.

Another possible cause of cyclic hematuria may be vicarious menstruation from the urinary tract but in this condition normal menstruation per vaginam will be present unless the vicarious menstruation is of the substitutional type. This type is exceedingly rare and occurs only following natural or induced menopause or after hysterectomy. There is no reason why vicarious menstruation should occur after cesarean section.

Because of the great rarity and the considerable interest of the syndrome of "menouria" following cesarean section, we would like to make a plea that every case encountered should be fully investigated and reported. It is only in this way that the pathogenesis of its unique features can be clearly understood. This may also help to clarify the question of the uterine isthmic sphincter which might be of importance with regard to the etiology of abortion and of primary dysmenorrhea.

Summary

1. A peculiar syndrome which may follow lower segment cesarean section is characterized by the presence of a vesicouterine fistula above the level of the internal os, the occurrence of vesical menstruation, the absence of vaginal menstrual periods, and the absence of urinary incontinence although the cervical canal is patent.

2. The name "menouria" has been coined to describe the vesical menstruation which is always the chief presenting symptom.

3. The few cases showing these typical features that have so far been reported in the literature are reviewed and a case of my own is described in detail.

4. Thorough investigation of my case has revealed that all the interesting features of this syndrome can be explained by the presence of a functional sphincter at the uterine isthmus.

5. The causes of the great rarity of the syndrome are discussed.

6. A plea is made that every case of this nature should be thoroughly investigated and reported.

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THE OCCURRENCE OF ANEMIA OF THE NEWBORN IN ASSOCIATION WITH THE APPEARANCE OF FETAL HEMOGLOBIN IN THE MATERNAL CIRCULATION*†

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CHOWN[3, 4] has presented evidence of fetal hemorrhage into the maternal circulation. The work to be reported is an attempt to assess the relative frequency of such hemorrhage. Though such an occurrence had been postulated by others,[18] proof was first obtained by Chown.

Procedure

Fetal erythrocytes contain a type of hemoglobin which is relatively resistant to alkali denaturation. This difference is the basis of the method of Brinkman,[1, 2] modified by Ponder, which we used.

The red cells are separated from the plasma, washed, packed, and hemolyzed with distilled water. Measurements of the optical density are taken at ten-minute intervals after addition of alkali until four or five consecutive readings are identical. It is assumed that denaturation is then complete. The logarithm of the percentage change of optical density is plotted against time and the original percentage of fetal hemoglobin is then determined by extrapolation to zero time.

In hemolysates obtained from a normal adult the logarithm of the concentration of undenatured hemoglobin drops rapidly to zero, denaturation being complete in twenty to thirty minutes. In samples containing fetal hemoglobin the drop is linear but composed of two components with different slopes, the rate of decrease changing abruptly at some point. When large percentages of fetal hemoglobin are present its concentrations in the original sample may be estimated by extrapolation to zero time. When small amounts are present extrapolation is not precise because of the small number of points obtained. A definite plateau is established, however, in many cases and fetal hemoglobin may be said to be present although its concentration may not accurately be determined.

Since the quantitation of fetal hemoglobin in concentrations of less than 10 per cent is subject to error, we sought to determine the qualitative reliability of the method at low concentrations. Mixtures of fetal and adult hemoglobin were made and tested by the method described. The upper left-hand graph in Fig. 1 shows a known negative control. The 1 per cent dilution sample does not show a definite change as compared with the control. The

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2 and 4 per cent samples show a plateau in addition to a definite prolongation in denaturation time. These curves were reproducible on aliquots of the same hemoglobin mixtures. Therefore, in the determinations which were made on patients the results were read as negative or positive rather than in percentages. As a result of our experimental dilution tests we felt that the method was sufficiently accurate to detect the difference between positive and negative blood samples but not sensitive enough to enable us to quantitate the amounts which we were encountering in the maternal circulation.

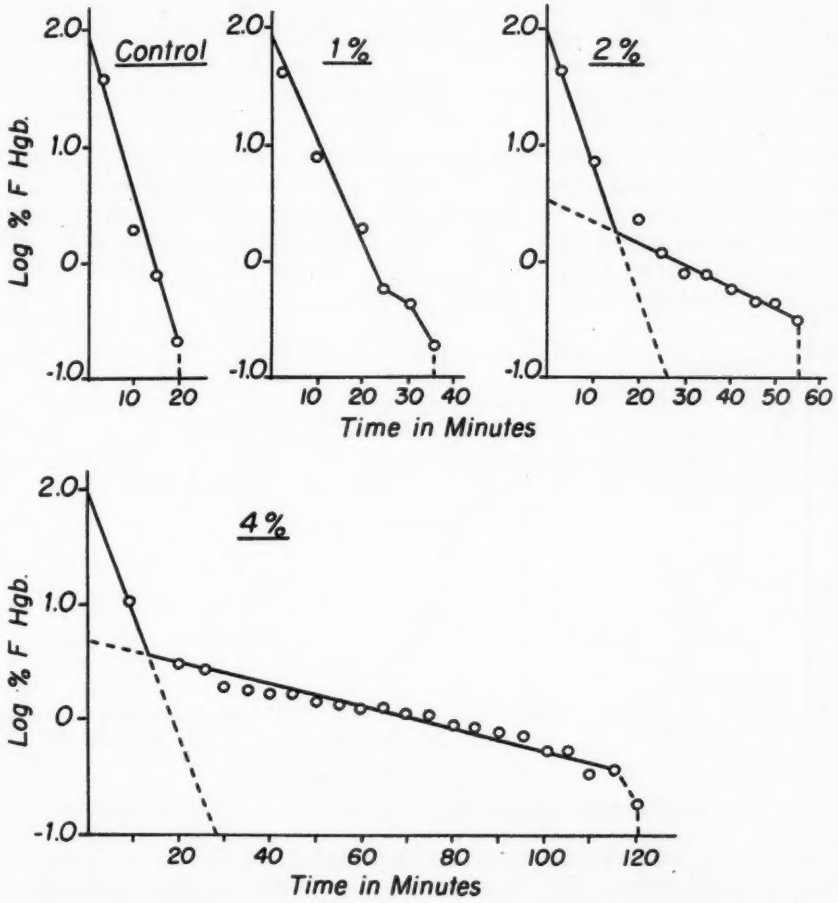

Fig. 1.—Alkali denaturation reaction. Mixtures of normal adult and fetal hemoglobin expressed as per cent of fetal hemoglobin added to adult hemoglobin.

Plan of Study

Spectrophotometric hemoglobin determinations were made on capillary blood of infants who appeared pale while in the nursery. Blood samples of the mothers of these infants were analyzed for fetal hemoglobin. Mothers demonstrating fetal hemoglobin were retested at intervals after delivery.

Eighty-six additional adults were tested for fetal hemoglobin. Eight were normal females and males. Seventy-eight were women whose blood was analyzed in the immediate postpartum period. The infants of 57 of these women had hemoglobin determinations performed within the first week of life.

Results

Twenty-four mothers were observed whose blood contained fetal hemoglobin during the immediate postpartum period. Twenty of these women have been available for follow-up study. The fetal hemoglobin had disappeared one to three months later in all but one woman. The initial capillary blood hemoglobin level in the infants of 17 of these women ranged from 18 Gm. per cent to 10 Gm. per cent. Two infants were noted to be markedly pale at birth but since their initial hemoglobin in the nursery was not recorded they will not be further considered in this paper. The infant born to the woman whose fetal hemoglobin has persisted had 20 Gm. per cent of hemoglobin at birth. In this instance no hemorrhage is thought to have occurred. Since the fetal hemoglobinemia in the mother has been persistently 14 per cent, this infant was also excluded from the series. The reason for the fetal hemoglobin in this case is not apparent.

Three of the 17 infants were type A and the mothers type O. One of these infants was considered possibly to have mild erythroblastosis fetalis due to A-O incompatability. We are mindful of the hemolysis which must occur in such major incompatabilities. The time interval after hemorrhage, however, may be an important factor in the ability to detect fetal hemoglobin in the maternal circulation after a bleeding episode.

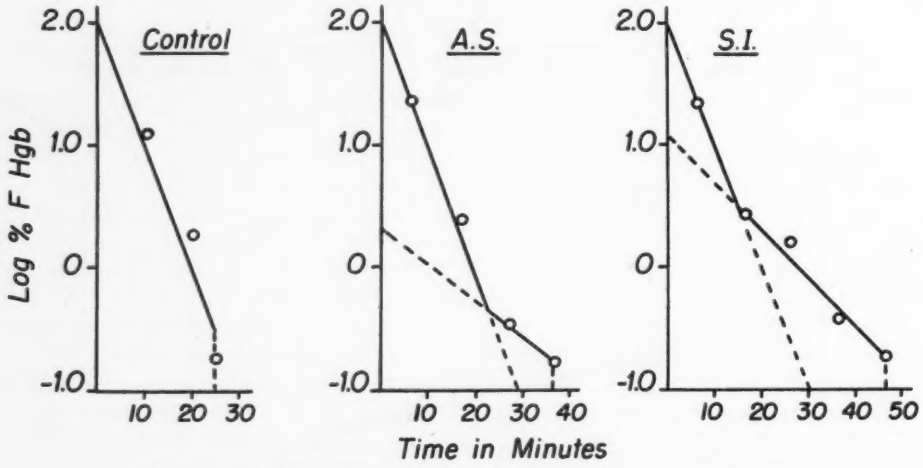

Fig. 2.—Patients with low values of per cent of fetal hemoglobin.

Figs. 2 and 3 show the denaturation curves observed in 5 of 17 women included in this series. These were samples with the least amount of fetal hemoglobin and are reproduced so that the reader may judge the validity of our decision that the tests were positive. They were chosen in order that we would not be guilty of biased sampling for demonstration purposes. Patient A. S. might be considered as being questionably positive. The other 4 graphs show a distinct difference as compared with the controls. The other 12 patients, not illustrated here, showed a more marked prolongation of denaturation time and a more horizontal plateau. The graphs on these 12 were of the type seen in our 4 per cent dilution studies. But, to repeat, we have merely interpreted all graphs as being positive or negative.

Table I shows the observed hemoglobin levels in these 17 infants as compared with a group of 24 control infants whose mothers showed no evidence of fetal hemoglobin. A mean difference between the two groups as great as that found would occur by chance less than one time in a thousand. The samples were obtained at various ages up to 5 days. The control infants were

sampled so that their ages were distributed in the same proportions. When the 3 infants with major blood incompatibilities were eliminated from the series the same statistical significance was found.

TABLE I. HEMOGLOBIN LEVELS OF INFANTS (GRAMS PER 100 ML.)

	NUMBER	RANGE	MEAN	S.D.
Infants of mothers with transitory fetal hemoglobinemia	17	10.0-18.0	13.3	2.6
Controls	24	13.5-24.6	18.1	2.8
Difference			4.8	
S.E. of difference			0.87	

P = 0.001

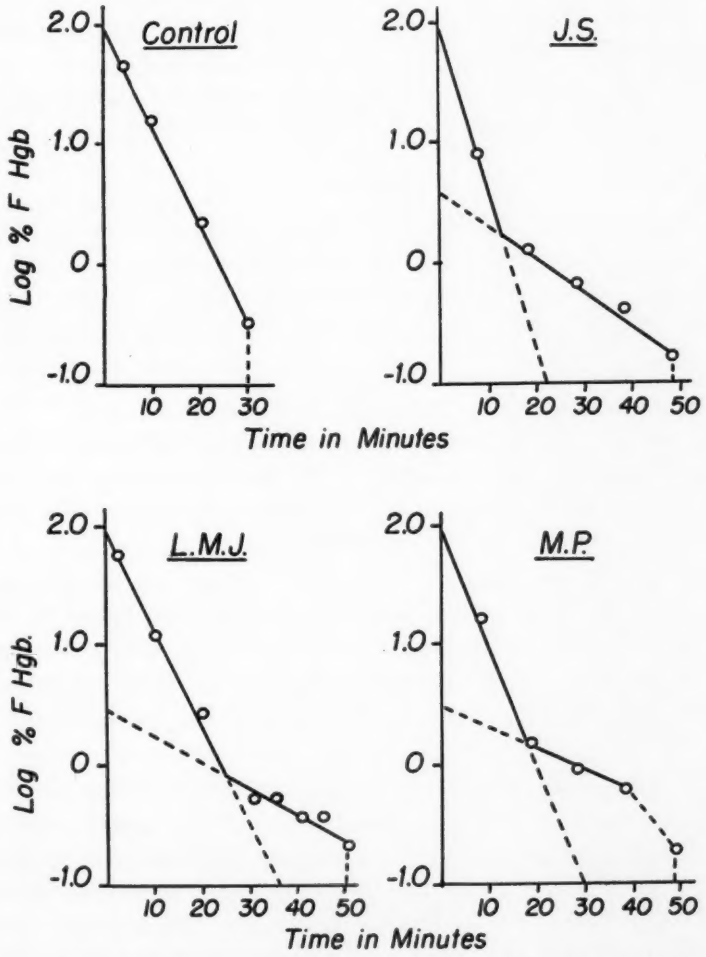

Fig. 3.—Patients with low values of per cent of fetal hemoglobin.

The various types of obstetrical complications noted in the 78 obstetrical patients who were used as controls are shown in Table II. The percentage of complications is high since at the beginning of this study we purposely chose patients with obstetrical complications in the hope of finding additional instances of fetal hemoglobinemia. The right-hand column lists the same data for the 17 infants with completed records whose mothers showed fetal hemoglobin shortly after birth.

TABLE II. OBSTETRICAL COMPLICATIONS IN HISTORIES OF 78 CONTROLS AND 17 ANEMIC INFANTS

	CONTROLS	ANEMIC INFANTS
Intrauterine death	1	0
Erythroblastosis fetalis	5	1
Placenta previa	2	1
Prolapsed cord	3	0
Elective section	5	2
Breech	2	0
Toxemia	0	1
Uterine inertia	1	0
Abruptio placentae	1	1
Twins	0	2
Total	20	8

An interesting observation is that 7 of the 17 infants whose mothers had fetal hemoglobin in their circulation were premature by weight.

In 3 of the cases we were unable to demonstrate by differential agglutination any evidence of fetal cells in the maternal circulation.

Comment

Previously reported experiments have shown that maternal red cells may pass the placental barrier and enter the fetal circulation. The old concept of integrity of the fetal and maternal circulations may be summarized by the following quotation from page 183 of the tenth edition of *Williams Obstetrics*.[6] ". . . there is no direct communication between the vessels of the chorionic villi and the intervillus space. The independence of the two circulations was most convincingly demonstrated, perhaps, during the first months of pregnancy by comparing the contents of the fetal vessels with that of the intervillus spaces. In the former, large numbers of nucleated red corpuscles are found, which are never present in the latter."

In 1941 Levine and his associates[9] stated, "Since the Rh factor . . . is probably limited to only red cells, it is assumed that fetal blood in one form or another penetrates the villus in sufficient quantity to induce immunization in the mother." Levine[8] calculated that as little as 0.067 c.c. of packed fetal cells crossing the placental barrier might establish Rh immunization in the mother.

The studies of Naeslund and his collaborators[12, 13] using radioactively tagged red cells and elliptocytes for transfusion into pregnant women demonstrated that red cells crossed from the maternal blood into the fetal circulation. Martland and Martland[10] studied the blood of 2 pregnant women who had committed suicide by inhaling carbon monoxide. They were not able to isolate carboxyhemoglobin in the infant. In view of the rapidity with which carbon monoxide is fixed to the red cells, they accepted this finding as proof that there is no transfer of red cells across the placental barrier.

In 1954 and 1955, Chown[3, 4] reported 3 cases of infants who bled prior to delivery. By means of immunological and hemoglobin-denaturation techniques, he felt that one of these cases demonstrated fetal bleeding into the maternal circulation. Mengert and his co-workers[11] reported the results of

their investigations into the problem of maternal blood entering the fetal circulation. Following the plan of Naeslund, they transfused pregnant women with red cells tagged with radioactive iron and sickle-cell trait cells. They were able to recover these cells from the fetal circulation.

The mechanism of transfer of red cells into either the maternal or fetal circulation may be related to the breaking off of portions of the villi. It has been known that this can happen. It is likely that in this way a varying amount of red cells may pass from one circulation into the other. This would require pressure differentials which Hellman[7] thinks may not exist. He suggests that the villi are active structures with protoplasmic microvilli. Under the electron microscope the pseudopods flow out and close in again and engulf droplets of plasma or red cells. Hellman sugests that such a mechanism of planocytosis is more in keeping with the volumes of red cells which have been reported to pass from the maternal circulation into the fetal circulation.

The investigations of Dempsey[5] have not demonstrated any instance of physical communication between the fetal and maternal circulation. These electronmicroscopy studies, limited to the study of normal tissue, have determined the barrier between the two circulations to be of 0.3 micron's thickness in the thinnest areas observed. It is possible that in some situations this layer of three cells may suffer interruption and that varying quantities of the circulation may mix.

In the alkali denaturation method described by Singer, Chernoff, and Singer,[16, 17] the normal adult level of fetal hemoglobin varies from 0 to 2 per cent. The denaturation technique used in this study failed to show the presence of fetal hemoglobin in 78 normal controls. Our dilution studies also indicated that with the method used fetal hemoglobin had to be in excess of about 2 per cent to be reliably detectable.

Using an immunological technique, Ruchnagel and Chernoff[14] have found that fetal hemoglobin in increased amounts may appear in the circulation of pregnant women. Such elevations occurred during the second trimester of pregnancy and were returning to normal at the time of birth. The levels which were observed were only slightly above 1 per cent. Because of the early rise and subsequent decline during the third trimester of pregnancy they felt that the increased amount of fetal hemoglobin represented a stress phenomenon in the mother.

None of the mothers reported here showed any evidence of a disease process which would stimulate the bone marrow. Since the immunological technique was not utilized in this study we cannot correlate the values obtained by Ruchnagel and Chernoff in pregnant women with the values obtained in this study. It should be noted they state that their technique is much more sensitive for detecting fetal hemoglobin than alkali denaturation.

All the cases encountered occurred between November, 1954, and March, 1956. During this period there were approximately eight thousand deliveries at Kings County Hospital. It is therefore apparent that the phenomenon reported by Chown may be relatively common.

The clinical picture presented by these infants varied from pallor to acute hemorrhagic shock, severe enough to require emergency blood transfusions in one of the 17 cases.

We wonder if some instances of death ascribed to asphyxia pallida may not be due to fetal hemorrhage during labor either into the maternal circulation or into the uterine cavity. Cervical blood was collected from 9 pregnant women who were admitted to the hospital with vaginal bleeding during the last trimester of pregnancy. Seven of these blood samples were positive for fetal hemoglobin. Four of these 7 patients gave birth to stillborn infants. The other three infants were apparently normal. Of the 2 women whose cervical blood samples were negative for fetal hemoglobin, one gave birth to a stillborn and the other to a normal infant.

Conclusion

In conclusion, we believe we have demonstrated an association between anemia in the newborn infant and fetal hemoglobin in the maternal circulation. One possible interpretation would be hemorrhage from the fetus into the maternal circulation. Another possible cause for the maternal fetal hemoglobinemia would be maternal stress. If the latter is the explanation, we find it difficult to correlate the anemia of the newborn with fetal hemoglobin in the mother.

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Discussion

DR. CARL T. JAVERT.—The subject of the admixture of fetal and maternal blood has been discussed in the literature for some two decades. As Dr. Kohl mentioned, most of the obstetric textbooks emphasize that the two bloods do not mix under normal circumstances. Paton also makes that statement in his textbook of embryology. Because of the tremendous importance of the Rh factor and the work of various investigators in that field, Levine and others, who showed immunologically that the two bloods apparently did mix, we felt it important to embark on a morphologic and histologic study of the possible mixture

of the two bloods. There are several men in this audience, including Dr. Douglas, Dr. Ball, and Dr. Schaefer, who have followed the studies in our pathology laboratory, which began in 1939. They were interrupted by World War II but results were finally published in Surgery, Gynecology and Obstetrics 94: 257-269, 1952. We investigated the possibility of such admixture in the fetal placenta. Our findings have since been confirmed by Kline. Dr. Kohl has added the chemical link in the growing chain of evidence that the two bloods do mix.

I wish to show a number of slides in which nucleated red cells and erythroblasts appear in the intraplacental hematomas. There are only two layers of cells separating the fetal from the maternal circulation. The trophoblastic barrier has ciliated cells as Dempsey, Wislocki, and others have pointed out with the electron microscope. The trophoblastic endothelial junction consists of these two layers of cells which separate the fetal from the maternal circulation. You can postulate that degeneration, rupture, traumatic rupture, perforation of these areas will permit fetal cells to enter the maternal circulation and produce some of the biochemical effects that Dr. Kohl has shown us so well tonight.

There is another time (in early pregnancy) that affords us opportunity to study morphologically the admixture of the two bloods. Up to 8 or 10 weeks' gestation the fetal blood has many normoblasts.

To summarize, the intervillous hematomas can be found in about 1 to 2 per cent of the therapeutic and nonintentional abortion material, and in perhaps 7 per cent of the spontaneous abortion cases. In premature and full-time infants, the incidence is upward of some 25 or 28 per cent. In other words, from the morphologic standpoint we are able to find intervillous hematomas in only up to 25 per cent of the placentas of normal infants, most of which seem to be of fetal origin. However, Dr. Kohl suspects from the chemical standpoint an admixture of 80 per cent. Such a high incidence was found morphologically in our cases of erythroblastosis fetalis.

DR. LOCKE L. MACKENZIE.—I was very much interested in the discussion and I should like to ask a question of a physiochemical nature. It is well known that if one takes serum from a pregnant woman around the twentieth week of her pregnancy, and differentiates that serum on concentrated phenol adjusted to an alkaline pH, he will find that all of the albumin will not be denatured, but all the globulin—both the alpha, beta, and gamma fractions—will be denatured. If one examines this same serum by the more conventional methods, such as out-salting or electrophoresis, he will find that the percentage of albumin and globulin is very different by these methods than it is by the method of denaturation. The question I want to ask Dr. Kohl is: Does he think there is a possibility that there may be some fetal hemoglobin in the specimen which might make the difference between these two findings which are obviously not compatible?

DR. WALTER J. O'CONNOR.—This study is the outgrowth of the observation of Chown, who reported in 1954 that he had studied 3 infants who were anemic at birth. He was able to detect fetal blood in the maternal circulation which subsequently disappeared.

What Dr. Kohl has presented may be considered strictly academic by some. But there is a great deal of practicality involved in this problem also. Pediatricians on occasion see infants who at birth show a progressive fall in hemoglobin during the first twelve to twenty-four hours of life. Some of these infants in the past have been considered to have erythroblastosis fetalis even though the usual laboratory data on such infants do not support such a viewpoint. I can recall one infant whose hemoglobin was noted to fall from 16 to 8 Gm. per cent in twenty-four hours. Laboratory tests failed to confirm the impression of erythroblastosis fetalis and yet this infant was subjected to an exchange transfusion because of our inability to explain the hemoglobin drop on any other basis. Dr. Chown's three patients were also given exchange transfusions.

This paper and Chown's report make it easier now to be more discriminating in the treatment of newborn infants who show progressive anemia in the first twenty-four hours of life. Certainly such newborn infants should be tested for evidence of hemolytic disease of the newborn and other more esoteric diseases, such as thrombocytopenic purpura.

If laboratory evidence for such diseases is lacking then one should bear in mind the possibility of fetal hemorrhage into the maternal circulation. The clinical picture may vary from pallor to hemorrhagic shock. But if this is borne in mind, some needless exchange transfusions may be avoided.

DR. LYMAN BURNHAM.—I think this is fine work that is being done to elucidate what we already know, namely, that fetal blood must get into the maternal circulation, and I believe that a big field is opened here to help us in the study of erythroblastosis, if not of other subjects.

I will be interested to hear what Dr. Kohl may find out in the future about when the fetal blood gets into the maternal circulation and specifically about the relationship of the reading he gets just before delivery with that just after delivery. I am anticipating that the readings after delivery will show a very much higher count than just before delivery because of the trauma of labor contractions on the capillaries of the chorionic villi. This has a practical bearing in cases of isoimmunization where each pregnancy is unusually important. The trauma of labor may increase the passage of fetal blood into the maternal circulation to such an extent that the increased sensitization so caused will seriously jeopardize future childbearing. Although cesarean section has gone out of vogue in the treatment of erythroblastosis, I believe it still has its place in these occasional cases. Not only can the patient thereby be easily delivered one, two, or even three weeks early, thus avoiding some of the intrauterine action of her antibodies, but in addition this additional sensitization is prevented that takes place I believe during labor.

I was hopeful that Dr. Kohl would have something to say about what permits the fetal blood to get into the maternal circulation. Maybe it is a two-way street but I never thought about its going the other way, namely, the maternal blood getting into the fetal circulation.

There is a question whether it is a normal thing for the placenta to permit passage of fetal blood into the mother and possibly this work can help to demonstrate whether it is normal or whether it is evidence of some deficiency. Since 1942, I have thought it was a vitamin C deficiency, but I was unable to support the very suggestive histories of these mothers of erythroblastotic babies with demonstrable evidence of an abnormal vitamin C absorption curve in pregnancy.

In any case there are now various preparations on the market that are designed to improve the integrity of the blood vessel walls. In addition to vitamin C, they contain hesperidin and/or other bioflavinoids.

DR. KOHL (Closing).—I may have allowed myself to be misunderstood about an 85 per cent incidence. I do not know what the true incidence is. This is a biased sample. We started with babies who were in difficulty. As Dr. Hall said, "I just delivered a baby that looked pale as the devil." He then collected blood from the mother, which was just reported to us, by telephone, as positive for considerable amounts of fetal hemoglobin. For this reason I can make no statement about the incidence of this condition. I know that Dr. O'Connor feels that, if our current observations withstand further investigation, we will be able to show this condition to be associated with anemia of the newborn much more frequently than other conditions which we have thought to be quite important.

Dr. Burnham, I do not know when the fetal blood gets into the circulation of the mother. We hope to be able to answer this question after further study. There has been so much contributed to the literature and to discussion on the timing of this transfer in erythroblastosis, and the effect of labor on initiating transfer, by people who are experts in the field, that I hesitate to make any comment. I really do not know what causes the fetal blood to go into the circulation. I am convinced, by what Dr. Javert has shown and by the slides prepared by Dr. Dempsey in his electron microscopy work, that a structure only 0.3 microns in thickness, containing either two cell layers under the light microscope, or three cell layers under the electron microscope, is a very fragile area and well may be the point of exchange.

We wish we could put radioactive cells into the infant and get them out of the mother. We are open to suggestions on how this might be done.

ARTIFICIAL HIBERNATION ("LYTIC COCKTAIL") IN THE TREATMENT OF ECLAMPSIA

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NEW drugs and methods have been proposed during the last few years to combat the dramatic signs and symptoms of eclampsia. We have been able to gather 24 of these drugs or methods in a recent review.[1] One of these new methods, the so-called "artificial hibernation," has been accepted with enthusiasm in some European and Latin-American countries. Its chief proponent, Laborit,[2] by means of a mixture of drugs (chlorpromazine, promethazine, meperidine) which he calls "lytic cocktail," aims to treat "the capillary impermeability and neutralize the incriminated chemical mediators, as well as the reticulo-histiocytic excitation."

The neuroplegic drugs, with or without refrigeration, are said to place the patient in a "disconnected" state, characterized clinically by hypothermia, hypotension, bradycardia, bradypnea, "twilight sleep, with unconsciousness, generalized muscular relaxation, loss of memory. . . ."[3]

Based on those hypothetical premises, and after the publication by Aoustin[4] of a report of the first case of eclampsia so treated, numerous authors[5-34] have been publishing their results, most of them unfortunately based on only a few observations. Also, the results are usually difficult to evaluate because of the variations introduced in: quantity of glucose solution used as diluent, composition of the "lytic cocktail," duration of "artificial hibernation," and use or omission of refrigeration. Nevertheless, from an analysis of 184 cases published in 31 papers, we might deduce tentatively the following facts:

A. Most authors employ drugs only, without refrigeration, some of them stating that the last mentioned is unnecessary.

B. The average duration of the "artificial hibernation" was 40 hours, with extremes between 22 and 76, according to one series of 19 cases.[12]

C. The average fall in blood pressure was 59 mm. in one report[21] and 36 in another.[27]

D. The temperature fell on an average to 96.8° F.

E. Some authors have found tachycardia at the beginning of treatment; others found only slight pulse modifications.

F. In one series of 46 cases,[27] 9 patients had more than 10 convulsions and 8 more than 20 before treatment. After medication, 28 had less than 10 and 18 more than 10 convulsions. In some small series an immediate cessation of convulsions was obtained, while one author[5] stated that the medication did not prevent further convulsive attacks.

G. There were 7 maternal deaths in 184 cases, representing a maternal mortality of 3.7 per cent.

H. The perinatal mortality was 18.9 per cent.

I. The chief complications were bronchial hypersecretion imputed to the promethazine, and puerperal psychosis (8 cases).

In view of the unsatisfactory results obtained with other drugs, and in spite of the purely theoretical basis of this new method, it was decided in our hospital to give the method a one-year trial. We are presenting here an analysis of 56 cases of eclampsia treated with a "lytic cocktail" from Feb. 15, 1955, to Feb. 15, 1956.

Method

We used only Laborit's "lytic cocktail" No. 1, with only half the dose of chlorpromazine proposed by the original author, without refrigeration, with the following composition:

Chlorpromazine	25 mg.
Promethazine	50 mg.
Meperidine	100 mg.
5% glucose solution	8 ml.

Half of the above solution was injected, as many times as seemed necessary from clinical considerations, always intravenously. Thus, we have injected from one to eleven doses and, as an average, 2.9. Deliberately, only small amounts of glucose solution were used as diluent, because from our past experience we gained the impression that large amounts of fluids made the condition of the eclamptic patient worse.

Results

In an attempt to evaluate the results, we are going to analyze the effects of medication upon the following: number of convulsions, blood pressure, pulse, temperature, maternal and perinatal mortality, as well as the complications observed.

1. Number of Convulsions.—Here we are taking into consideration only the convulsions observed in the hospital. In most cases treatment was started after the first hospital convulsion. In 41 per cent there were no convulsions after treatment, and in 59 per cent we noticed from 1 to 17 postmedication convulsive attacks. The average number of convulsions before medication was 1.4 and post treatment, 2.8.

2. Blood Pressure.—The effects upon the blood pressure are variable and in our cases we noted:

A. In 43 per cent there was an average systolic fall of 80 mm. The blood pressure reached a normal level and remained there in 20.9 per cent (Fig. 1); in 22.1 per cent the initial fall was transient, and the pressure reached later a level even higher than before medication, even though the patients were still under the action of the drugs. In 2 cases the fall was sudden and marked (from 160 to 0, and from 150 to 32), and in the first case the patient presented cyanosis, temporary cardiac arrest, and apnea, requiring artificial respiration by means of intratracheal intubation.

B. In 38 per cent an irregular effect was observed (Fig. 2).

C. In 18 per cent we noted a blood pressure increase.

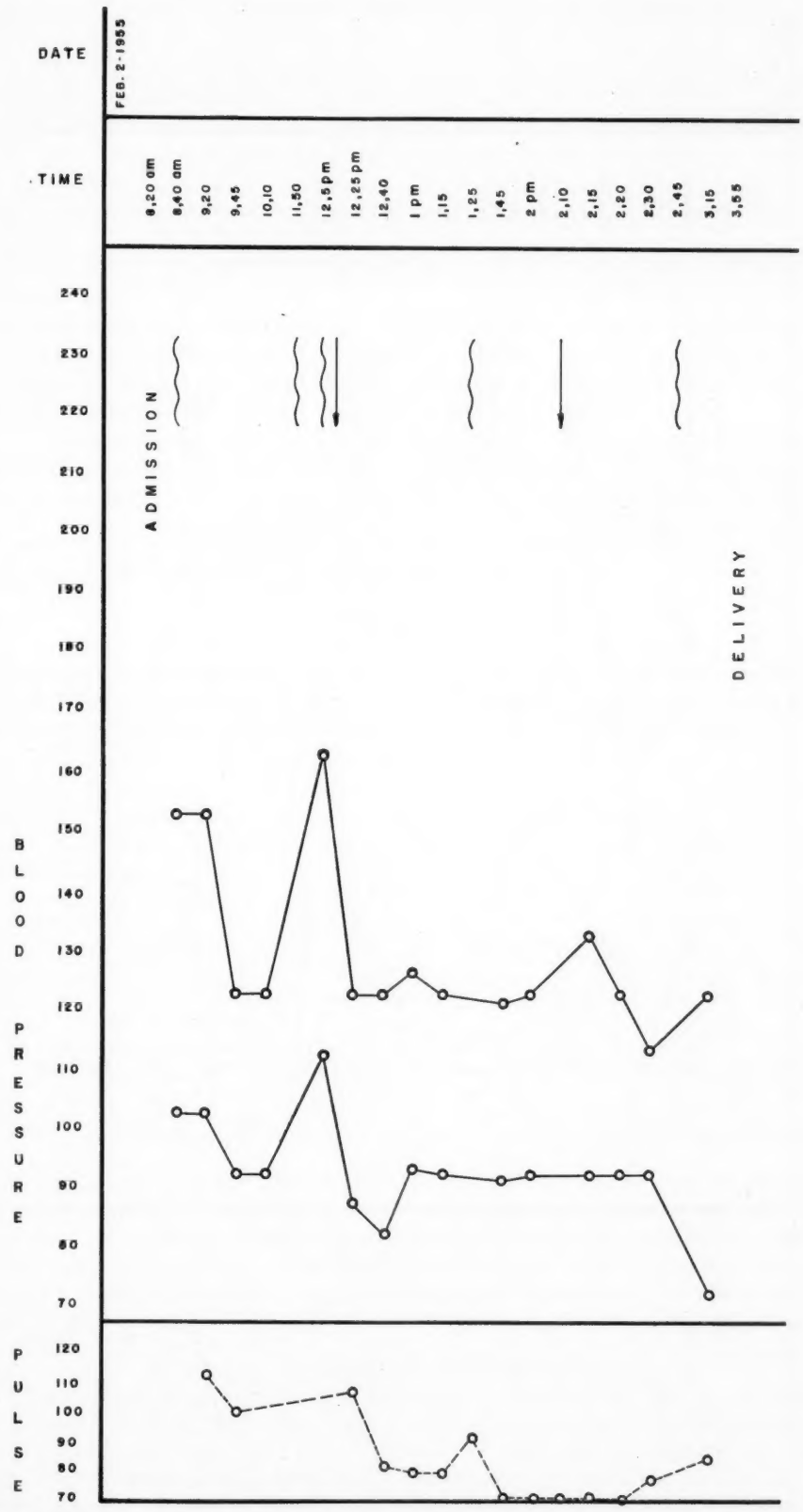

Fig. 1.—Case 1. Sustained normal blood pressure after medication. Wavy line represents convulsion, arrow, "lytic cocktail."

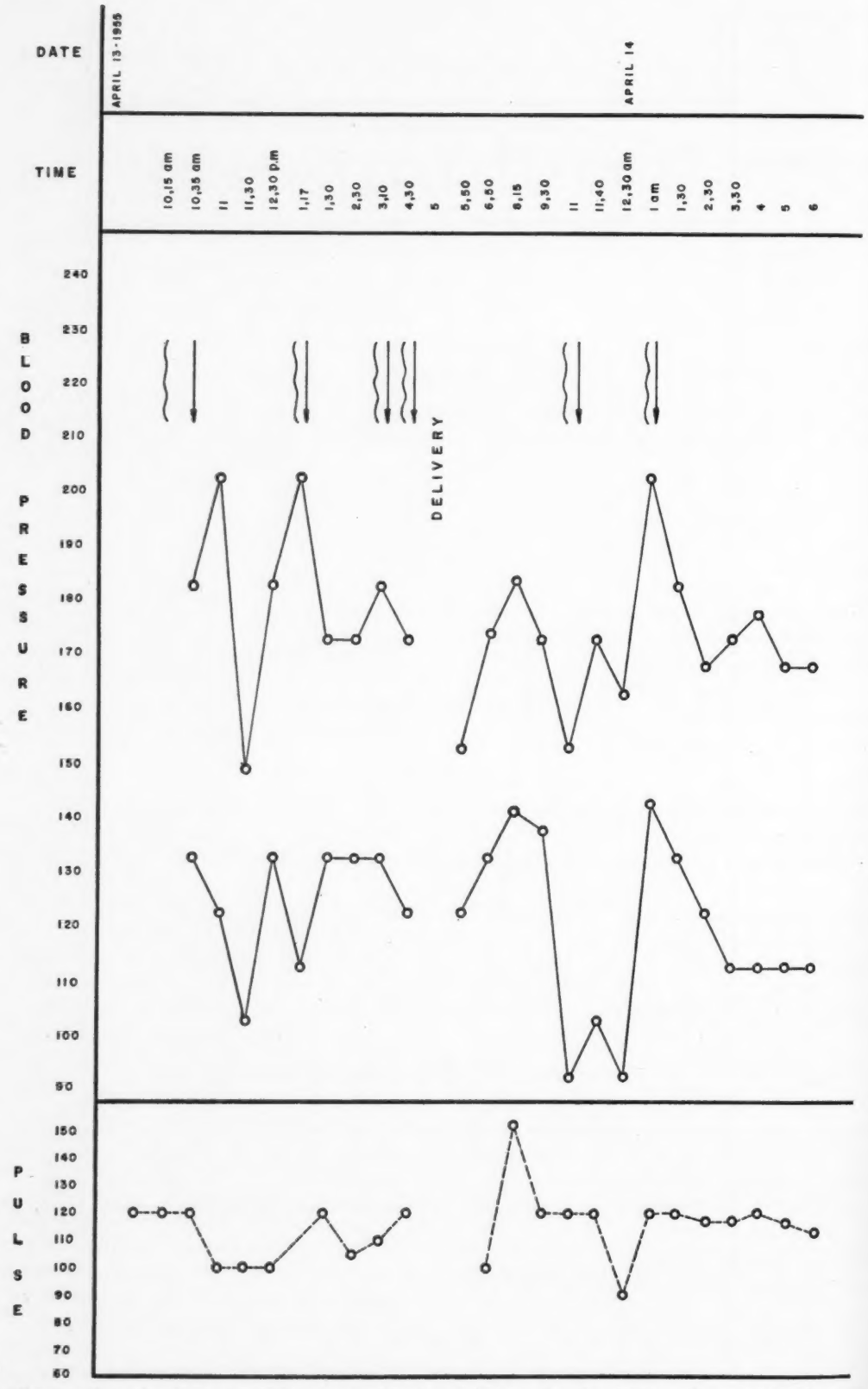

Fig. 2.—Case 2. Irregular effects upon blood pressure and pulse. Wavy line represents convulsion, arrow, "lytic cocktail."

3. Pulse.—The action upon the pulse was also variable. We observed tachycardia in 58 per cent, but this tachycardia was present before medication; in 25 per cent there were irregularities with periods of brady- and tachycardia; a normal pulse was observed in 16 per cent of the cases.

4. Temperature.—The effect on body temperature was hardly constant either. In only 2 cases was there a definite decrease to 95 and 95.2° F., respectively.

5. Maternal Mortality.—Three mothers died, a maternal mortality of 5.4 per cent.

6. Perinatal Mortality.—In all, 58 babies were born, of whom 14 were stillborn and 3 died in the immediate postnatal period. Thus the perinatal mortality was 29.3 per cent. All these deaths occurred in premature babies of whom 2 weighed less than 1,000 grams (750 and 650, respectively).

7. Complications.—We observed 6 cases of uremia, 4 cases of puerperal psychosis, 2 cases of sudden and marked hypotension, and 1 case of pneumonia.

Among these complications the high incidence of puerperal psychosis, mentioned in other publications, deserves special attention, especially when compared with past experience in our hospital in which only 3 cases of puerperal psychosis were observed in 348 cases of eclampsia.

Comment

Lack of knowledge on the etiology of toxemias of pregnancy has led to empiric trial of numerous drugs. The "lytic cocktail" is one of the most recently proposed, based also chiefly upon theoretical considerations.

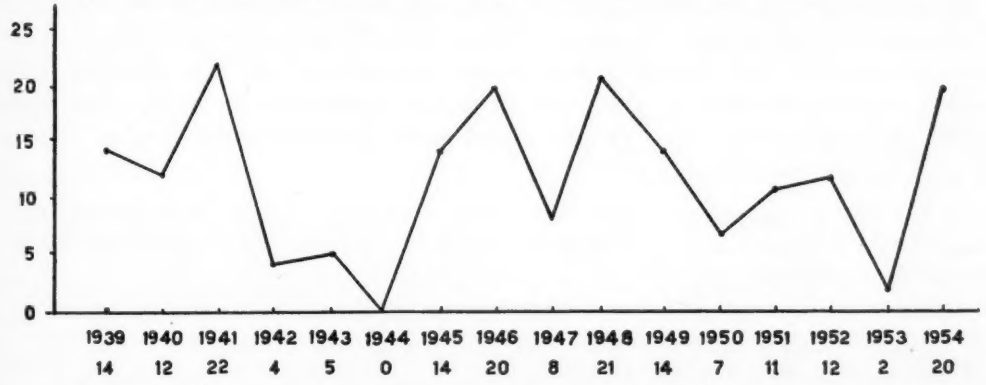

Fig. 3.—Maternal mortality from eclampsia in the Concepción Palacios Maternity.

The effects of the "lytic cocktail" upon convulsive attacks, blood pressure, pulse, and temperature are very variable, without any definite pattern which can be imputed, with reasonable certainty, to the medication employed.

In spite of the lack of constant effect upon various factors which have been analyzed above, there is no question in our minds but that in the majority of the cases prompt clinical improvement can be observed after treatment with the "lytic cocktail" is started. Recovery from coma appears to be faster than with any other treatment tried by us thus far.

The maternal mortality (5.4 per cent) obtained in our present series is low when compared with the total maternal mortality from eclampsia in our hospital (11.7 per cent from 1939 to 1952), or with the same mortality obtained in groups of cases on which we have tried other treatments, as may be seen in Table I.

However, our present series is small and we do not find justification for drawing any solid conclusion, especially when we think of the spontaneous variations in maternal mortality from eclampsia, as we have observed it in the Concepción Palacios Maternity (Fig. 3).

Our perinatal mortality (29.3 per cent) clearly shows that nothing is to be expected from this treatment on the fetal side.

Furthermore, the "lytic cocktail" is not without side effects, and in our series we have observed marked hypotension and puerperal psychosis.

While unbounded enthusiasm for this method of treatment seems to us premature, the clinical improvement together with the apparent lowering in maternal mortality and the relative paucity of cases seem to us to justify fully further trial in larger series.

TABLE I

TREATMENT	NO. CASES	DEATHS	
		NO.	%
Morphine and magnesium sulfate	73	6	8.2
Magnesium sulfate	23	2	8.4
Thiopental	49	8	16.3
"Lytic cocktail"	56	3	5.4

Summary

An analysis is presented of 56 cases of eclampsia treated with a "lytic cocktail" in the Concepción Palacios Maternity in Caracas. The effects of this medication on the number of convulsions, blood pressure, pulse, and temperature are analyzed. On none of these was there a constant effect. Maternal mortality (5.4 per cent) was low in comparison with that obtained with other treatments used in the same hospital. Perinatal mortality was high (29.3 per cent). The chief complications were sudden hypotension in 2 cases and puerperal psychosis in 8.

We wish to thank the resident staff of the Concepción Palacios Maternity for their cooperation; Palenzona & Co. for the drugs used in this trial; and Dr. Marcel Roche for his constructive criticism.

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MERCURIAL DIURETICS IN TOXEMIA OF PREGNANCY WITH SODIUM AND POTASSIUM STUDIES*

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THE etiology of pre-eclampsia-eclampsia being unknown, specific therapy directed at the etiological agent is impossible. In spite of the enormous amount of investigation of the disease in recent years, treatment must still be symptomatic, directed toward one or more of the following signs: edema, hypertension, and proteinuria. Thorough prenatal care, with early recognition and appropriate treatment of signs and symptoms of oncoming toxemia, affords the greatest opportunity of halting its progression and keeping maternal and fetal mortality and morbidity at a minimum. Earliest of the signs of impending toxemia are abnormal gain in weight and appearance of edema, which usually precede the development of hypertension. The basic etiology of this process is undetermined, but the physiological pathology is recognized as an alteration in sodium and water metabolism resulting in abnormal sodium and water retention.

A generally accepted preventive measure directed at this pathological fluid retention is restriction of salt intake. Specific therapy directed toward the mobilization and excretion of the accumulated sodium and water has been commonly practiced, the chief method being production of acidosis by administration of ammonium chloride.

In surveying the problem, we were impressed by the effective use of mercurial diuretics in the mobilization of edema and sodium in congestive heart failure. The literature was searched for references to the clinical use of such therapy in the management of toxemia of pregnancy. On the basis of their studies of the effectiveness of various agents in producing sodium excretion in pregnant women, Brown and Bradbury in 1948 suggested clinical trial of mercurial diuretics in toxemia.

The primary action of organic mercurials is on the renal tubules. Bartram and Christian have shown that when a mercurial diuretic is injected directly into a renal artery of one kidney, that kidney responds with diuresis while the opposite kidney shows no change in function. The source of the excreted fluid, for the most part, has been shown to be the extracellular

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spaces. The literature is replete with reports of the use of mercurials in edema associated with cardiac failure, and their toxic effects and contraindications have been well defined. A "low-salt" syndrome due to excessive losses of water and salt has been described in cardiac patients who have been given mercurial diuretics. In our experiences we agree with Schemm, who found that if adequate fluid intake is maintained mercurials are relatively harmless, even in the resistant edema or oliguria of renal disease. A complete review of the pharmacodynamics of mercurial diuretics has been presented by Ray and Burch.

In summary, the rationale for the initiation of mercurial therapy in toxemia of pregnancy is the premise that one of the fundamental disorders in pre-eclampsia is an abnormal electrolyte balance, characterized by retention and accumulation of sodium and water in the body. Because of the effectiveness of organic mercurials in promoting sodium and water diuresis we have chosen these drugs for therapeutic evaluation in toxemia of pregnancy. Thiomerin* was used in the majority of our cases.

The indications for therapy with mercurials have been excessive weight gain and development of pitting edema in pregnant women. Selected patients were admitted to the toxemia ward of Charity Hospital where first base line weight and urinary output determinations were recorded, and a thorough workup, including blood chemistry determinations and renal function studies, was done. Blood pressures were recorded at 1 to 4 hour intervals. A low-salt diet containing approximately 0.7 Gm. of sodium, 4.1 Gm. of potassium, and 1.6 Gm. of chloride was prescribed, and sedation ordered if indicated. Fluid intake and output were recorded daily, and daily before-breakfast weights and albumin determinations were noted. Some of the patients admitted from oupatient clinics had received ammonium chloride and mild sedatives, and had been instructed to restrict their salt intake. Failure to respond to this regimen resulted in their admission to the hospital.

It should be stressed that good results from mercurial therapy will be obtained only if the patients have shown sudden weight gain and pitting edema. Early in our series improper selection of patients led to poor results.

It has been our routine to use a dosage of 2 c.c. intramuscularly, and no toxic effects have been noted in any of our patients. On two occasions we have obtained amniotic fluid prior to delivery, twenty-four hours after the administration of mercurial. Neither of these specimens showed any trace of mercury. It is thought possible that mercury, which combines with albumin in the body, is unable to cross the placental barrier because of its large molecular size.

Usually from one to three injections have been effective, and long-term therapy as in congestive heart failure has not been necessary. This provides an additional margin of safety and perhaps explains the complete absence of toxic effects in our series.

Classification of the results of treatment has included good, fair, poor, and impossible to evaluate, with gradings made on the basis of weight loss and/or increased urinary output. It is felt that weight loss represents the best basis for evaluation of therapy since it is less subject to nurse and patient error than other criteria, such as urinary output. No attempt has been made to analyze blood pressure effects, since most patients received adjunctive

*The Thiomerin used in this study was provided by Wyeth Laboratories, Inc.

therapy directed toward this symptom, including bed rest and sedation. Statistics on fluid intake are not listed, as patients had fluid ad libitum and intakes before and after administration of the mercurial did not differ significantly.

This paper reports upon 100 consecutive cases of pre-eclampsia treated with mercurial diuretics. Analysis of the individual cases discloses that when weight loss and/or increased urinary output is considered, good results occurred in 75 patients, fair in 7, poor in 10, and 8 cases were impossible to evaluate. The 10 poor results occurred early in the series, in cases in which the drug was not indicated by our criteria—patients who were not edematous or who had been "dried out" prior to mercurial therapy. The results of therapy in 8 cases could not be evaluated as delivery occurred shortly after injection.

Table I presents the 82 cases in which the results were graded as good or fair, indicating their demonstrable responses to mercurial therapy.

TABLE I. AVERAGE WEIGHT LOSS IN KILOGRAMS IN 82 PATIENTS WITH FAIR OR GOOD RESPONSE TO MERCURIALS

NO. PATIENTS	NO. INJECTIONS	WEIGHT LOSS (KG.)	AVERAGE PER CENT INCREASE IN OUTPUT
49	1	2.59	165.5
30	2	3.04	67.7
2	3	3.07	111.0
1	4	8.98	89.9

In summary then, all of the evaluated patients treated, who met the criteria for therapy, had good or fair results, with evidence of benefit as noted in Table I.

Electrolyte Studies

In order to show more succinctly the results of the use of mercurial diuretics in toxemia, we have made flame photometer analyses of sodium and potassium levels in serum and urine of patients prior and subsequent to injection of the mercurial. These studies have been made in 24 patients.

Also 29 pre-eclamptic patients and 39 normal pregnant patients have had sodium and potassium studies of blood and urine in order to compare these data in normal and toxemic pregnancies.

Blood was collected from the antecubital vein in sodium-free Pyrex tubes. Twenty-four-hour urine specimens were studied and total 24 hour output of sodium and potassium calculated.

TABLE II. AVERAGE SODIUM AND POTASSIUM LEVELS IN SERUM AND URINE IN THE 39 NORMAL PREGNANCIES COMPARED WITH AVERAGE VALUES IN 29 PRE-ECLAMPTIC PATIENTS

	AVERAGE VALUE, NORMAL NONPREGNANCY	AVERAGE VALUE, NORMAL PREGNANCY	AVERAGE VALUE, PRE-ECLAMPSIA
Serum Na (meq./L.)	135-147	129.9	129.63
Serum K (meq./L.)	3.5-5.5	4.05	4.0
Na in Gm./24 hr. urine specimen	174-218	135.0	103.0
K in Gm./24 hr. urine specimen	64.1-76.9	33.4	29.5

Considering first the 39 controls, or normal pregnant patients, Table II shows that the serum sodium in milliequivalents per liter averages 129.9, consistently falling well below the nonpregnancy normal of 135 to 147 meq. per liter. No measurable difference is demonstrated between normal pregnancy and nonpregnancy levels of serum potassium, our patients averaging 4.05 meq.

per liter compared with a normal nonpregnancy range of 3.5 to 5.5 meq. per liter. Urinary sodium output, however, in normal pregnant patients is definitely below that of the nonpregnant, the normal range being 174 to 218 meq. per 24 hour specimen. Our pregnant patients averaged only 135. There is also a lowered output of potassium in pregnant individuals, our patients excreting an average of 33.4 meq. compared with a normal range of 64.1 to 76.9 meq. per 24 hour specimen.

Next, considering the pre-eclamptic patients studied, we can make the following observations concerning their sodium and potassium levels. In this group of 29 pre-eclamptic patients, no significant statistical difference could be shown between their serum sodium and potassium values and those of the normal pregnant patients just described. Urinary studies, however, demonstrated an even greater tendency toward sodium and potassium retention in pre-eclamptic than in normal pregnant patients.

On the basis of this group of cases, 39 normal pregnant and 29 pre-eclamptic patients, the following observations are possible: (a) both normal and toxemic pregnancies are associated with a lowered serum sodium level; (b) in both normal and toxemic pregnancies there is a lower than normal sodium and potassium excretion per 24 hour urine specimen, the retention of these two electrolytes in patients with toxemia being particularly marked.

Further studies were made by the flame photometer on 24 of the pre-eclamptic patients after injection of 2 c.c. of mercurial intramuscularly. Urine specimens were collected for 24 hours prior and 24 hours subsequent to injection of the mercurial and the total of sodium and potassium in milliequivalents excreted in each period was determined. Serum was collected prior to injection of the mercurial and 24 hours afterward, and sodium and potassium in milliequivalents per liter were calculated in each. Results are shown in Table III.

TABLE III. RESULTS IN 24 PATIENTS BEFORE AND AFTER INJECTION OF MERCURIAL DIURETIC

	AVERAGE VALUE BEFORE MERCURIAL	AVERAGE VALUE AFTER MERCURIAL
Serum Na (meq./L.)	129.37	129.7
Serum K (meq./L.)	4.0	4.02
meq. Na/24 hr. urine specimen	108.0	290.0
meq. K/24 hr. urine specimen	30.0	37.2

These values indicate little difference in serum sodium and potassium, and in urine potassium, but there is a marked increase in the sodium in the urine after injection of the mercurial.

Table III shows the postmercurial changes in output of sodium in the urine, giving an average of 168.5 per cent increase in sodium output over the premercurial 24 hour specimen.

Summary

1. One hundred cases of pre-eclampsia in which mercurial diuretics were used in therapy are presented. Benefit, as evidenced by weight loss and/or increased urinary output, is evaluated.

2. Sodium and potassium studies on blood and urine of 39 normal and 29 pre-eclamptic pregnant patients are reported, demonstrating:

a. Almost identical lowered serum sodium levels in both these groups as compared to nonpregnant normal individuals.

b. A decreased excretion of sodium and potassium in urine in both groups, especially marked in the pre-eclamptic patients.

3. Studies of sodium and potassium in the blood and urine of 24 pre-eclamptic patients before and after receiving injections of a mercurial diuretic are reported, demonstrating a marked increase in sodium output after administration of the mercurial.

Conclusion

On the basis of this study, we recommend mercurial diuretics as an adjunct to therapy in cases of toxemia of pregnancy with sudden excessive weight gain and pitting edema. It is believed that these drugs are efficacious and harmless in the dosages used.

No toxic effects were noted in 100 patients.

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THE TREATMENT OF PRE-ECLAMPTIC EDEMA WITH ACETAZOLEAMIDE (DIAMOX)*†

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EDEMA to many doctors means the accumulation of fluid beneath the skin of the lower leg in sufficient degree that pressure marks are visible. Vogl[16] defined edema as the accumulation in the body of an excessive amount of fluid which may be intracellular, extracellular, or both. Up to recent years, doctors thought that the abnormal fluid accumulations were restricted to the extracellular compartments, especially tissue spaces and serosal cavities, with the edema visible (from slight puffiness to massive anasarca) or invisible or occult (revealed by only weight gain or loss). We[6, 7] know now that retained fluid and electrolyte are never restricted to one body compartment but that there is an adjustment between the various body compartments with all of them taking part in the increases or decreases, as the case may be. Invisible, occult, or hidden edema[5] may amount to as much as 10 liters retained in the legs and thighs of a 70 kilogram woman without any pitting being demonstrable. There may be as much as 20 kg. of water and electrolyte lost after the birth of a baby without the patient's ever having shown any visible edema.

Diuretic drugs, especially the mercurial compounds, have been very efficacious in promoting a loss of water and electrolyte in patients with edema due to cardiac decompensation. They are less effective in some types of acute and chronic glomerulonephritis and even less in patients with abnormal accumulations of fluid in the serosal cavities. Dieckmann[5] has reported that the mercurial and other diuretic drugs were of no value in the treatment of pre-eclampsia-eclampsia. Brown and Bradbury[4] reported in 1948 that intravenous injections of larger amounts of mercurial drugs would produce a diuresis. We have confirmed this work but the diuresis, primarily of water, was always of short duration with a subsequent retention of sodium and water (the rebound phenomenon of Assali). We have not been able to remove all excess water and electrolyte from a patient with true pre-eclampsia nor have we been able to cure such a patient of her associated hypertension and proteinuria by the use of diuretic drugs.

Extensive studies of the pharmacology and clinical effect on edema of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide or acetazoleamide (Diamox)[9–14, 17]

*Supported in part by the Fiftieth Anniversary Fund for Eclampsia.
†Presented at a meeting of the Chicago Gynecological Society, Dec. 21, 1956.

have been reported. It can be given intravenously but oral administration is the route of choice. Diamox has apparently a very low toxicity and sensitization is rare, although death due to agranulocytosis has been reported. Belsky[3] stated that "Diamox alone or in combination with mercurial injections had little diuretic effect in the presence of anasarca and renal decompensation. However, after removal of ascitic fluid, the effectiveness of Diamox appeared to be increased, although supplementary mercurial injections were required."

Assali and co-workers[2] concluded, "In normal pregnancy, Diamox induced metabolic acidosis which was accompanied by increased excretion of water, Na, and K and a diminished excretion of ammonia, titratable acids, and Cl. These effects lasted for one or two days despite continuation of treatment. A 'rebound phenomenon' with water and electrolyte retention occurred after cessation of therapy. In toxemia of pregnancy, Diamox induced a more sustained water, Na, and K excretion. The excretion of Cl was not depressed. The 'rebound phenomenon' was longer than in normal pregnancy."

"The presence of this 'rebound phenomenon' and the inability to overcome it by altering the dose of Diamox or by changing the schedule of its administration seems to limit the usefulness of this compound in the management of toxemia of pregnancy."

"Loss of more water than solute during Diamox administration was observed in both groups of patients. Absolute values for electrolyte excretion were significantly less in toxemia than in normal pregnancy during all of the periods of study.

"Upon inhibition of renal carbonic anhydrase by Diamox, potassium was more readily available for excretion than sodium."

Schnieden[15] concluded that the incidence of signs of pre-eclamptic toxemia was significantly lower in 26 patients who received 250 mg. Diamox every third day in addition to a low sodium diet (1.2 Gm. or 52 meq. sodium daily) than in a control group of 24 patients who received a placebo. No differences occurred if the diet contained 3.0 Gm. or 131 meq. of sodium.

Ashe and associates[1] administered 250 mg. of Diamox to 100 patients with various signs of toxemia of pregnancy. The drug was given for 5 days, with rest for 2 days, and the regimen repeated until delivery. Unfortunately, no statement is made as to the duration of the pregnancy or of the drug therapy. The blood pressure decreased in 59 and increased in 10. Edema decreased in 59 and increased in 21; weight decreased in 82 and increased in 31. There were 2 premature stillbirths, 1 neonatal death, and 4 (delivered elsewhere) unknown. The authors concluded that, "Diamox is an effective and innocuous diuretic drug. It has been found to be useful in the treatment of pre-eclampsia, edema, and excessive weight gain due to water retention. In 32 patients with mild pre-eclampsia, there was a reversal of the disease and a dramatic readjustment of the patient's renal and vascular status with a loss of all signs and symptoms of pre-eclampsia. In several, the signs and symptoms of pre-eclampsia recurred at a later date. Twenty patients with excessive

weight gain who had made an adequate response to Diamox had a return of weight gain and/or edema when the drug was discontinued. Four of these patients developed pre-eclampsia. This indicates the necessity for the continuation of the drug even though an adequate clinical response has occurred."

In our studies with acetazoleamide (Diamox), again we noted that we were not able to remove all the abnormal retention of water and electrolyte in patients with pre-eclampsia, either because we did not have sufficient time (patients went into labor or the pregnancy had to be terminated) or the fluid is held differently. A few patients with presumably typical mild pre-eclampsia who were able to concentrate the sodium ion satisfactorily and who we thought had pseudo-pre-eclampsia, lost all their water and electrolyte in the antepartum period as a result of diet with or without Diamox. We believe our data show that one can remove a certain amount of water and electrolyte amounting to 500 to 2,000 Gm. in a period of 24 to 72 hours and in the period of 7 days, as much as 11 kg., in patients who do not have true pre-eclampsia but it will usually recur.

A possible explanation of our failure to cure patients with true pre-eclampsia may be that some of the retained fluid is intracellular and is not released until 24 to 72 hours after expulsion of the placenta. The use of hydrocortisone in a few patients seems to offer a method by which fluid and electrolyte can be transferred from intra- to extracellular compartments where there is an opportunity to cause its excretion.

To date we have given Diamox to over 200 pregnant patients but are reporting 148 periods of study on 106 patients. The majority were ambulatory and were seen once or twice each week by the same doctor during the period of study. All patients either had more than the normal amount of visible edema and/or had gained more than an average of 1.0 kilogram per week. It is obvious that we cannot be certain that the ambulatory patients took the Diamox.

All patients who were hospitalized were placed in a room in which the temperature and humidity were constant. The patients could have as much water to drink as they wished but careful measurements were made of all intake and output. If there was a urine volume of less than 1,500 ml. or oliguria, the patient was put on a schedule necessitating the ingestion of 200 ml. of water every hour while awake. Beam balance weights were obtained twice daily. The diet contained 211 mg. (9 meq.) of sodium, 981 mg. (25 meq.) of potassium, 400 mg. (11 meq.) of chloride, 47 Gm. of protein, and 1,521 calories.

Doses of Diamox ranging from 250 to 1,000 mg. were given to patients on regular diets or on low sodium and potassium diets. The final dosage was 500 mg. for a patient who weighed less than 80 kilograms, and 750 mg. for one who weighed more, given every second or third day.

Table I shows that Diamox with the restricted diet resulted in greater and more rapid losses in weight. Since 27 of the ambulatory patients gained weight, it is most likely that they did not take the drug; for all hospitalized patients on Diamox and diet therapy showed no such gains. It is worth noting that fewer patients on the restricted diet and Diamox gained weight than on Diamox alone.

TABLE I. NUMBER OF PERIODS OF TREATMENT OF 1 TO 28 DAYS' DURATION

LOST OR GAINED (GRAMS)	DIAMOX		DIAMOX AND LOW Na AND K DIET	
	GAINED	LOST	GAINED	LOST
1-499	5	2	-	1
500-999	3	17	5	4
1,000-1,499	6	6	2	6
1,500-1,999	2	7	1	4
2,000-2,499	3	17	-	7
2,500-2,999	--	5	-	6
3,000-3,499	--	6	-	4
3,500-3,999	--	2	-	12
4,000-4,499	--	2	-	5
4,500+	--	3	-	5
Total periods	19 (23%)	67	8 (13%)	54

Table II shows the mean antepartum weight loss during Diamox and diet therapy. The patient with pre-eclampsia loses much less weight.

TABLE II. WEIGHT LOSS IN 7 TO 10 DAYS

	ANTEPARTUM WEIGHT LOSS (MEAN IN KILOGRAMS)
Pre-eclampsia*	0.8
Hypertensive disease	2.3
Abnormal gain and/or edema (no toxemia) Range 0.4-9.2	2.6

*1 to 5 days.

Table III shows the periods of pregnancy when Diamox was administered. There were 106 patients who had edema and/or abnormal gain in pregnancy, 50 before the thirty-fifth week of pregnancy of whom 10 developed pre-eclampsia. Sixteen patients were known to have hypertensive disease. In the remaining 29 patients, possibly the loss of water and electrolyte prevented the subsequent development of pre-eclampsia. We noted that these patients had marked losses in weight and we concluded that in such patients in whom the water was still mobile (readily removed) there was little likelihood of pre-eclampsia occurring.

TABLE III. DIAMOX ADMINISTRATION AT DIFFERENT PERIODS IN PREGNANCY

PERIODS OF GESTATION (WEEKS)	PRE-ECLAMPSIA	HYPERTENSIVE DISEASE	ABNORMAL GAIN AND/OR EDEMA (NO TOXEMIA)
22-23		2	3
24-27	5	1	3
28-31		5	9
32-35	5	3	14
36-37	3		11
38-39	2	5	31
40+	1		3
Total 106	16	16	74

Table IV shows the duration of Diamox administration. Most of these patients received the drug daily or every other day. Prolonged daily administration of 500 mg. or more of Diamox caused no toxic effects on the fetus. It is not possible to determine how much improvement resulted from administration extending over 2 weeks. We also cannot state that we prevented the development of pre-eclampsia although we have the belief that water and electrolyte retention is reversible in the early stages of this disease.

Toxic effects in the patients were few in number. A transient dermatitis occurred in 2 patients and another had pruritus. Nausea was noted by one patient. Two patients had tingling or numbness of the arm or face. Stopping of the drug resulted in rapid cure.

There were no maternal deaths in the series. Two neonatal deaths occurred, one at term and the other at 26 weeks (erythroblastosis). Diamox had nothing to do with either death.

Three patients with twin pregnancy and edema and 3 patients with polyhydramnios with edema (none had pre-eclampsia) lost an average of 4.2 kilograms in one week with Diamox and low sodium and potassium diet treatment. Two patients with twin pregnancy and pre-eclampsia lost 0.5 kilogram in one week.

TABLE IV. DURATION OF DIAMOX ADMINISTRATION

DAYS	TREATMENTS
1-2	38
3-5	20
6-9	56
10-13	5
14-20	13
21-34	7
35-48	2
71-95	6
112*	1
	148

*Cardiac patient.

The results of Diamox administration are best shown by illustrative cases.

R. I., an 18-year-old Negro primigravida, had typical pre-eclampsia and, as is characteristic of these patients once they have reached a certain stage of the disease, the kidney was unable to concentrate sodium and because of the impaired water excretion, the total amount of sodium excreted per 24 hours was small (22 meq. per day). As the data in Table V indicate, 500 mg. of Diamox for 2 days did not cause an appreciable increase in the urinary sodium but did cause an increase in urine volume. The weight decreased by the same amount in the control and Diamox periods. However, within 24 hours after delivery of the placenta, the 24 hour urine contained 408 meq. of sodium. During the last 4 antepartum days the patient excreted 108 meq. of sodium in 8,930 ml. of urine, but in the first 4 postpartum days she excreted 1,080 meq. of sodium in 22,200 ml. of urine.

TABLE V. R. I., TYPICAL PRE-ECLAMPSIA IN A PRIMIGRAVIDA

DAY	DAILY CHANGE IN WEIGHT (KILOGRAMS)	EDEMA	URINE PER 24 HOURS					TREATMENT
			VOLUME (ML.)	Na (MEQ.)	Cl (MEQ.)	K (MEQ.)	PROTEIN (GM.)	
− 5	85.17	++++						
− 4 and 3	−0.77	+++	1,325	22	24	23	5.6	Control
− 2 and 1	−0.88	+++	2,640	31	47	33	4.5	Diamox daily
0	A.P. 81.86	+++	4,120	62	93	61	6.0	Delivery
	P.P. 73.98	++						
+ 1 and 2	−2.25	++	7,780	408	439	50	3.1	
3 and 4	−2.26	+	3,320	132	142	38	1.6	
5 and 6	−0.67	+	2,710	48	73	39	1.3	
7 and 8	−0.52	0	2,360	50	81	32	1.3	
+ 9	62.70							
(13.6 kilogram loss of water and electrolyte)								

B. H. was a 23-year-old gravida iv, para iii, white patient who was accepted from another hospital at 30 weeks' gestation. She had gained 7 kilograms within one week and ankle edema began 10 days before admission. The blood pressure was 150/100, edema was 4 plus involving the anterior abdominal wall, and the proteinuria was 4 plus (7.5 Gm. per 24 hours). She had had frequent headaches. Although she was at 30 weeks' gestation by menstrual history the uterus was the size of a 36 weeks' pregnancy.

Although this patient had some hypertension, 7 Gm. of protein in the urine per 24 hours, and marked edema, with minimal ophthalmoscopic findings, after we noted the relatively large amount of sodium excreted in the urine we felt that she did not have preeclampsia. We were uncertain about her diagnosis, thinking of some renal lesion. Finally, because of the large size of the uterus and relatively small size of the fetal head, we thought there might be a large placenta and a baby with hydrops. Patients with an erythroblastotic baby frequently have edema but we have never encountered one with this amount.

As shown in Table VI, on a low sodium and potassium diet the patient was losing weight and excreting large amounts of sodium in the urine. Both Diamox and Thiomerin caused tremendous increases in the sodium excretion but did not cause an increase in the urine volume to the same degree. The patient lost 11.3 kilograms before delivery and the weight loss at delivery amounted to 5.98 kilograms, of which the baby and placenta comprised 3.57 kilograms. On the day of delivery the patient still had a 1 plus edema. Seventy-two hours later the edema was ± and she had lost an additional 2 kilograms. The edema was definitely absent on the sixth postpartum day.

TABLE VI. B. H., MARKED EDEMA AND PROTEINURIA IN A MULTIPARA. DIAGNOSIS (?)

DAY	DAILY CHANGE IN WEIGHT (KILOGRAMS)	EDEMA	URINE PER 24 HOURS VOLUME (ML.)	Na (MEQ.)	Cl (MEQ.)	K (MEQ.)	PROTEIN (GM.)	TREATMENT
-13	84.30							
-12 and 11	-0.35	++++	1,230	61	22	9	7.5	Control
-10 and 9	-1.98	+++	2,915	247	151	34	5.0	Diamox on 10th
8 and 7	-1.40	++	1,815	156	126	31	4.1	Diamox on 8th
6	-1.27	++	1,090	129	166	11	1.7	Thiomerin, 2 ml.
5	-0.28	++	1,850	146	66	26	3.6	Diamox
4	-1.05	++	980	20	39	16	2.9	
3 and 2	-0.50	+	1,025	46	63	9	3.2	Thiomerin on each day
1	-0.32	+	660	4	9	14	2.5	
0	A.P. 73.20	+	1,060	11	20	10	4.1	Delivery
	P.P. 67.22							
+1 and 2	-0.70	+	1,325	8	12	2	0.7	
3, 4, and 5	-0.81	±	1,943	46	62	21	1.1	
6	-0.32	0	2,110	41	36	23	1.2	
8	62.10						1.0	
Baby	1,720 grams	Antepartum weight 73.20 kilograms						(16.22 kilogram loss of water and electrolyte)
Placenta	1,850 grams	Postpartum weight 67.22 kilograms						
	3,570 grams						5.98 kilograms	

The blood pressure never exceeded 150/100 except during delivery when it rose to 180/120 and it was within the normal range after the first 48 hours. The proteinuria varied but was always quite marked and although the patient lost weight it is obvious that the decrease in the edema had no effect on the proteinuria.

Table VII shows the relevant blood chemistry determinations. Note the low hematocrit and serum protein due to hemodilution and the increase, especially rapid, in serum protein as edema was lost after delivery. Since the nitrogen balance was negative it seems

probable that the more rapid increase in protein over hemoglobin is due to a return of plasma proteins from the extracellular space to the vascular system. We had noted that the extracellular fluid contained small fibrin clots. The patient was on a low sodium (less than 9 meq. average) and potassium (less than 25 meq.) diet containing a maximum of 1,600 calories and 47 Gm. of protein.

TABLE VII. B. H., BLOOD CHEMISTRY

DAY	HEMATOCRIT (VOL. PER CENT)	SERUM PROTEIN (GM. PER CENT)	Na (MEQ. PER LITER SERUM)	cl	K
-13	27	5.2	141	104	5.2
9	29	4.4	134	101	4.6
4	29	4.5	132	108	4.6
1	29	5.0	128	111	5.1
Delivery					
+6	29	5.1	137	102	4.7
+9	30	6.0			

The serum electrolytes were normal on admission. The decrease in sodium and increase in chloride were due to the repeated doses of diuretic drugs. We believe that this patient would have followed the same course without diuretic drugs. The blood nonprotein nitrogen was 29 mg. per cent on admission and the urea clearance on antepartum day 4 was 58 per cent of normal and on postpartum day 8 was 64 per cent.

We believe this case is an example of a marked water and salt retention with the resultant hypertension, proteinuria, and edema; if neglected or not properly treated there is no reason why convulsions, coma, and death might not ensue, either from the resultant toxemia or from cardiac failure. We do not believe this patient had typical pre-eclampsia because a case with this degree of proteinuria, edema, and hypertension in a period of 13 days would have shown a marked increase in severity necessitating immediate delivery or the baby and/or the mother would have died.

V. T. was a 24-year-old primigravid Negro patient referred to us. At 35 weeks' gestation she was found to have gained 16 kilograms and her blood pressure was 150/110 with a 3 plus proteinuria. In the hospital she was on a low sodium and potassium diet in the climate room. After a 3 day control period she was given 750 mg. of Diamox daily for 6 days. She lost an average of 0.8 kilograms per day as compared with a 1.1 daily weight loss in the control period. The proteinuria and blood pressure remained unchanged. The large amount of sodium in the urine in the control period seems to indicate that the patient did not have pre-eclampsia. There was some increase in urine sodium produced by the Diamox but the urine volume showed a proportionately greater increase. She was delivered by cesarean section at 37 weeks' gestation of a 2,895 gram normal baby. This patient lost 14 kilograms but never had edema. The final diagnosis was hypertensive disease with a question mark.

TABLE VIII. V. T., HYPERTENSIVE (?) DISEASE IN A PRIMIGRAVIDA

DAY	DAILY CHANGE IN WEIGHT (KILOGRAMS)	URINE PER 24 HOURS					TREATMENT
		VOLUME (ML.)	Na (MEQ.)	cl (MEQ.)	K (MEQ.)	PROTEIN (GM.)	
-13	79.95	500 inc.	34	31	2	0.2	
-12 and 11	-0.95	2,320	116	52	51	0.4	
10, 9, and 8	-1.43	3,180	129	82	50	0.5	Diamox daily
7, 6, and 5	-0.90	2,786	44	55	39	0.6	Diamox daily
0	A.P. 73.30	2,440	27	34	10	5.3	Delivery
	P.P. 68.51						
+1 and 2	-0.25	2,215	18	24	18	4.5	
+3 and 4	-0.19	2,345	77	54	16	3.3	
9	65.50						
(9.66 kilogram loss of water and electrolyte—no visible edema)							

C. P. was a 38-year-old gravida viii, para vi, Negro patient who was referred to the hospital because of blood pressure of 190/120 and 1 plus proteinuria. She had no edema and her weight had been constant for a month (diet and ammonium chloride therapy). She had had stillbirths in 1948 and 1949, and the pregnancies in 1950, 1951, and 1952 were complicated by hypertension. She was placed on a low-sodium and potassium diet and after 3 days was given 750 mg. of Diamox daily for six days. There was possibly a greater weight loss with Diamox than with diet alone (Table IX). The urine volume increased considerably but there was only a slight increase in the excretion of sodium which had been adequate before the Diamox. The blood pressure had already become stabilized at near normal levels prior to the administration of Diamox. Chloride excretion roughly paralleled that of sodium. The potassium balance was always positive. The patient was delivered at 33 weeks by cesarean section of a 2,445 gram baby who survived. The diagnosis was hypertensive disease in pregnancy.

TABLE IX. C. P., MULTIPARA WITH KNOWN HYPERTENSIVE DISEASE

DAY	DAILY CHANGE IN WEIGHT (KILOGRAMS)	URINE PER 24 HOURS					TREATMENT
		VOLUME (ML.)	Na (MEQ.)	Cl (MEQ.)	K (MEQ.)	PROTEIN (GM.)	
-18	80.55						
-17 and 16	-0.52	1,715	73	72		0.3	
15, 14, and 13	-0.73	2,596	80	48		0.2	Diamox daily
12, 11, and 10	0.43	2,990	41	42		0.3	Diamox daily
0	A.P. 76.45	1,980	72	67		0.6	Delivery
	P.P. 73.43						
+1 and 2	-1.11	1,850	57	34		1.1	
+3, 4, and 5	-0.25	1,403	14	8		0.9	
+6	69.62						
(7.93 kilogram loss of water and electrolyte—no visible edema)							

Comment

Whether the primary cause of pre-eclampsia is vasoconstriction or an abnormal water and electrolyte retention is still a moot point. Proteinuria, per se, is certainly not the cause. There is no question about the occurrence of abnormal gain in weight which must, because of the amount and rate of change, be due to retention of water and electrolyte, with or without clinical edema.

Since visible or occult edema is one of the principal signs of pre-eclampsia, its elimination should cure pre-eclampsia and its prevention might eliminate pre-eclampsia. Early attempts at dehydration by saline catharsis or sweating were of no use. Acidifying salts have only been stopgaps.

Our studies as well as those of others have shown that Diamox is a relatively safe diuretic. In pregnant patients with their normal edema or with abnormal weight gain and/or edema due to various causes other than pre-eclampsia, administration of Diamox will cause varying degrees of loss of weight together with an increased urine volume and sodium elimination. A diet very low in sodium and potassium will have the same result but may require slightly more time. The combination of Diamox and diet is more effective. If the patient remains on the diet, in many cases edema will not recur and in those in whom it does the accumulation is slow.

Patients who had true pre-eclampsia as characterized by the usual signs together with a slow elimination of sodium and water showed a poor response

to Diamox or to Diamox and diet. We were not able to eliminate all edema until several days after the expulsion of the placenta. Possibly, had there been sufficient time before spontaneous labor ensued or the severity of the case necessitated termination, we might have been able to dehydrate them to their normal weight. We believe that there is a prodromal stage of pre-eclampsia when conditions are reversible; Diamox and other diuretic drugs are effective in this period. When pre-eclampsia once becomes established, however, the fluid retention is irreversible until the placenta has been expelled.

Calculations of the fluid and electrolyte compositions of extra- and intracellular fluids based on balance studies and studies with radioactive Na_{22} indicate that, although all excess water has been eliminated, there is still an abnormal sodium balance which requires weeks or months to return to normal.

Pregnant patients with edema and/or abnormal weight gains who lost weight rapidly did not have true pre-eclampsia and this condition did not develop in such patients. Thus the response to Diamox administration may be used as a crude test to determine the seriousness of visible or occult edema (weight gain).

We had hoped that once the edema had been eliminated the patient could be permitted a higher sodium intake by balancing with Diamox; unfortunately this plan has not functioned.

Limited experience with our low sodium and potassium diet throughout the last 24 weeks of pregnancy has demonstrated that not only can the normal edema of pregnancy be prevented but the exacerbation of hypertensive disease (so-called superimposed pre-eclampsia) can be prevented.

Summary

Diamox caused mild symptoms or signs in 4 patients (3 per cent). Since it is a sulfonamide, the possibility of precipitation in the kidney as well as leukopenia must be kept in mind.

Diamox is a relatively safe drug for producing weight loss by increasing urine volume and urine sodium in pregnant patients with visible or occult edema (abnormal weight gain), pseudo-pre-eclampsia, hypertensive disease, and decompensated heart disease.

Diamox has comparatively little effect on patients with true pre-eclampsia.

The use of Diamox has some prognostic value in that a marked loss of weight due to a considerable increase in volume of urine and sodium excretion would suggest to us that the patient did not have pre-eclampsia-eclampsia but had water and electrolyte retention due to some other condition, possibly the pregnancy itself, multiple pregnancy, anemia, hypertensive disease, etc.

The Diamox was furnished by Dr. J. D. Gallagher of the Lederle Laboratories Division of the American Cyanamid Company.

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Discussion

DR. LESTER D. ODELL.—It seems from this work that the elimination of excessive water with sodium from the pregnant patient is a highly desirable objective. The authors report an apparent clinical improvement in toxic patients, after the removal of edema, and we are left with the feeling that if sodium chloride (salt) could be sufficiently reduced in the diet of pregnant patients early enough, toxemia of pregnancy, like pestilence and war, might become a thing of the past.

I have used acetazoleamide (Diamox) since 1954. My patients receive 250 or 500 mg. per day of the drug from the inception of administration until delivery. The longest duration of treatment was 144 days in a case of primary edema, or, as the essayists state, one of "pseudo-pre-eclampsia." The patient improved on Diamox but became symptomatically worse without the drug. It has been a clinical impression that drying patients out before delivery with Diamox shortens labor and lessens blood loss.

Does Diamox constitute the definitive diuretic agent for the treatment of edema in toxic patients? In the ambulatory patient, visiting the doctor's office, taste and ease of administration are extremely important for any drug, for the patient may neglect to take an offensive or inconvenient medication. I believe, therefore, for the office practice, acetazoleamide (Diamox) is superior to ammonium chloride or exchange resins whenever limitation of sodium in the diet alone fails to correct water retention. In addition, I favor its use over mercurial diuretics because it has always seemed hazardous to use mercury on a set of kidneys whose exact physiologic or pathologic status cannot be accurately determined for three to six months after delivery. However, when the patient is hospitalized, where activities can be controlled, bowels regulated, diet accurately weighed, and medications given on schedule, taste and ease of administration seem less important.

In the 12 hours after admission to a hospital, considerable weight is lost by the average toxic patient with nothing more than bed rest and a bowel cleansing. Most of this weight is lost in the form of water from lungs, skin, bowels, and kidneys, and should be considered highly available water in superficial extracellular spaces, mucous surfaces, and in sweat glands. Possibly after the first 24 hours a diuretic agent may be evaluated, although insensible loss continues at a lessened rate via lungs, skin, and bowels.

Several years ago we were interested in exchange resins, a quite successful diuretic for hospitalized cases. Our patients received from 60 to 120 Gm. of the resin daily by mouth. Comatose patients were given resin enemas. Some toxicity was observed. We rarely treated the patient over five days and managed a maximum weight loss of 22 pounds in one case. The patients selected for treatment seemed to be more completely dried out with exchange resins than those in this study. I would like to inquire if the essayists have treated the same patient concurrently or serially with Diamox and exchange resins. Diamox inhibits carbonic anhydrase, thus preventing reabsorption of water from the kidney tubules, increasing acidosis, and thereby increasing diuresis. Exchange resins, on the other hand,

remove sodium via the intestinal tract, liberating water, largely from the kidneys, with a compensated acidosis but without much elevation in urinary sodium. Inasmuch as the mechanism of action is so different, if the objective is to remove water and sodium, the drugs could be used concurrently or serially.

The essayists state, "Pregnant patients with edema . . . who lost weight rapidly did not have true pre-eclampsia. . . . Thus the response to Diamox administration may be used as a crude test . . . ," the contention being that we have again introduced another "test" for a disease complex, pre-eclampsia-eclampsia, whose identification and classification leave much to be desired. As I see it, certain pregnant patients develop a vascular syndrome characterized by various degrees of hypertension with or without significant proteinuria and with or without edema or evidence of water retention. It is true that a small minority of these patients may have nephritis or pre-existing hypertensive disease, but the great majority of cases develop during pregnancy, and therefore constitute a true toxemia of pregnancy. As I understand it, the authors would classify this large group as pre-eclampsia-eclampsia whenever the patient cannot handle sodium chloride, and as essential hypertension whenever sodium is eliminated in large enough amounts in urine. What is confusing is that either group can develop eclampsia (convulsions and coma) and end up with either maternal or fetal death. I am also confused by the statement that if a patient with pre-eclampsia can be carried with that disease for fourteen days or more, she did not have that disease because she should have been delivered, have had convulsions, have had a dead baby, or be dead herself if she had had it. The introduction of two new terms, pseudo-pre-eclampsia, and superimposed pre-eclampsia, further this confusion.

DR. CHARLES FIELDS.—Diamox is an oral diuretic that inhibits the action of carbonic anhydrase enzyme in the renal tubules, consequently prompting the renal excretion of base, namely, sodium and potassium. It decreases the exchange of hydrogen ions for sodium ions both directly and via the ammonia cycle. The net effect is that fewer hydrogen ions are liberated by the renal tubule cells. Fewer hydrogen ions are available for excretion into the renal tubule lumen and, therefore, sodium ions are substituted. Most of the sodium is then excreted with bicarbonate and the urine becomes alkaline. The excretion of sodium carries water with it, and diuresis results. Since potassium ions normally compete with hydrogen ions for excretion via the same tubule mechanism, this drug causes also an increase in excretion of potassium ions. The end result is a hyperchloremic acidosis. Upon cessation of the administration, the salutory effect again returns after 2 to 3 days. Such action appears to limit its usefulness.

The authors have tested this drug and have shown its limitations not only in its mode of action but in the treatment of edema in true preeclampsia. Toxemia is a disease peculiar to pregnant women, and the diagnosis is based on the presence of hypertension, edema, and proteinuria. Adequate and strict attention to abnormal weight gain prenatally is essential. If such a patient is placed on a suitable diet and given Diamox, toxemia may be prevented. But once a diagnosis of toxemia is established, hospitalization is imperative. This the authors have pointed out. Failure in this may jeopardize the life of the mother and her infant. Those of us who attend the maternal mortality meetings see examples of such laxity all too often.

Since we already have enough difficulties when a woman develops toxemia, I wonder how practical it would be to the clinician to have the term "pseudo-pre-eclampsia" re-introduced.

Patients who attend the Toxemia Clinic at the Cook County Hospital are evaluated, and if they show the earliest signs of toxemia, e.g., blood pressure of 140 systolic and/or 90 diastolic, with or without edema or proteinuria, they are hospitalized. Consequently, we see many such cases. Because of lack of facilities and personnel, we are unable to study our patients as minutely as the authors can. However, we terminate the pregnancy when the patient fails to show a clinical improvement.

On our service we attempt to induce labor regardless of the period of gestation or the status of the cervix. Our procedure is to rupture the membranes and allow all the

fluid to drain off. This is followed by intravenous Pitocin. If at the end of 6 to 8 hours labor is not well established, the pregnancy is terminated by cesarean section. We have a significant series of vaginal deliveries in which the results have been excellent. I should like to know what criteria the authors use for terminating pregnancy by cesarean section?

Finally, it seems to me that a diet containing 211 mg. sodium, 981 mg. potassium, 400 mg. of chloride, with 47 Gm. of protein is a very low diet. What is such a diet? And how long could you maintain a patient on such a diet without her seeking morsels of food elsewhere?

DR. DIECKMANN (Closing).—The statement was made that we are confusing toxemia of pregnancy by introducing new terms. Pseudo-pre-eclampsia, refers to those patients who have edema and/or abnormal weight gain, usually with only slight hypertension and/or proteinuria and who appear to have mild pre-eclampsia. These patients, when given repeated intravenous injections of hypertonic sodium chloride solution do not develop severe cases because they are able to eliminate the sodium ions. These, too, are the patients who, when given a diuretic drug or placed on a restricted sodium intake, will lose 2 to 3 kilograms of weight in 5 to 7 days. We cannot state that if these patients were not treated they would not ultimately develop pre-eclampsia but to date none have. Thus the patient who loses 2 to 3 kilograms in a week from a diuretic drug need not restrict her salt intake.

Superimposed pre-eclampsia is a term not introduced by me. Conceivably it can occur but I believe it rarely does. The patient with prepregnancy vascular-renal disease frequently has an increase in the hypertension and/or the proteinuria about the twenty-sixth to the thirty-second week of gestation. We believe that this is merely an exacerbation of her renal condition.

We have tried resins but the difficulty is that they are unpalatable in the large amounts required and the pregnant patient differs from the patient with heart or kidney disease in that she feels well and sees no need to take the huge daily doses necessary. We have not been able to compare Diamox with resins because one rarely if ever has a chance to have the edema reaccumulate in pregnancy as it does in heart and kidney disease.

We do not expect the ambulatory patient to be on the low-sodium and potassium diet because it is very difficult for her to achieve that low an intake. In the hospital it can be done and a few ambulatory patients have also remained on such a diet for as long as 6 weeks. Usually, the diet is limited to 3 to 4 weeks. The ambulatory patient saves her urine for 24 hours on the day before she comes to the office, measures the urine, and brings a small bottle in for the determination of sodium and we can in that way determine how effectively she is following our instructions. The patient cannot have a high-protein intake and a low-sodium diet because of the sodium content of the meat.

The pre-eclamptic patient who does not lose weight or in whom the blood pressure and proteinuria remain high or increase is delivered vaginally, if the cervix is "ripe," by rupture of the membranes. If the cervix is not "ripe" and the patient is obviously not improving, she is delivered by cesarean section, preferably under local anesthesia. It is unwise to subject these patients to repeated attempts at induction with intravenous Pitocin drip.

Since the abnormal weight gain of ultimate pre-eclampsia begins in the second trimester of pregnancy, that is the time when attention should be given to the dietary intake of the patient and if diuretic drugs are of no avail she should be hospitalized for 4 or 5 days and taught the proper kind and amounts of food which she should eat daily for the remainder of her pregnancy. This will reduce the incidence of pre-eclampsia-eclampsia.

MATERNAL BLOOD AND CEREBROSPINAL FLUID ESTIMATION FOLLOWING THE ADMINISTRATION OF CHLORAL HYDRATE DURING THE PUERPERIUM

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PREVIOUS studies have demonstrated the absorption and metabolism of chloral hydrate from the rectum when the drug is administered in suppository form. Its presence in the maternal blood, breast milk, amniotic fluid, and fetal blood has been determined.[1, 2, 3]

Material and Method

Twenty-five unselected patients were included in the present study. They were women recently delivered in the maternity wards of Jefferson Medical College Hospital. In all instances cerebrospinal fluid studies were indicated because of a positive serologic reaction observed during the pregnancy. In no case was there central nervous system disease. All studies were made on the third postpartum day.

The patients were given the medication at varying intervals (from 30 minutes to 10 hours, 30 minutes) before the cerebrospinal fluid was obtained. Chloral hydrate was administered in the form of a rectal suppository, 1.2 Gm. A nurse inserted the medication and cautioned the patient that it was for medicinal purposes and not as a laxative. At the designated time following administration of the drug a lumbar puncture was performed on the patient. Clear, colorless fluid was obtained in all instances. The specimen (5 c.c.) was placed in a sterile tube containing penicillin to inhibit bacterial growth. At the same time 5 c.c. of blood was obtained. Complications were minimal and consisted entirely of postpuncture headache.

Results

All routine examinations (cells, proteins, serologic test for syphilis, colloidal gold curve) of the spinal fluid were found to be within normal limits.

Table I presents the values obtained for the concentration of chloral hydrate and its metabolites in the blood and cerebrospinal fluid. The amounts of chloral hydrate and trichloroacetic acid in the cerebrospinal fluid are small. The corresponding blood levels of these substances are much greater due to their poor passage through the "blood-brain barrier." Urochloralic acid passes into the cerebrospinal fluid in substantial quantities. Exceptionally large quantities of urochloralic acid were demonstrated in Patients 3 and 6. These patients were suffering from severe pre-eclampsia with evidence of liver damage.

The concentration of trichloroethanol in the cerebrospinal fluid is variable, but in general is less than that of urochloralic acid but higher than that of

TABLE I. CONCENTRATIONS OF CHLORAL HYDRATE AND ITS METABOLITES
(EXPRESSED IN MICROGRAMS PER MILLILITER)

	PATIENT NO.																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Time	30 min.	30 min.	1 h.	1 h.	1h. 30	2 h.	2 h. 15	3 h.	3 h. 15	4 h.	4 h. 30	4 h. 30	5 h.	5 h.	5 h. 15	5 h. 15	6 h.	6 h.	6 h.	7 h.	7 h.	8 h.	9 h.	9 h. 30	10 h. 30
Blood.—																									
Chloral hydrate	2.5	7.5	0	3.5	9	5.5	5	11	7.5	20	10	30	12	12	7.5	19	12	15	8	19	3	20	3	10	20
Trichloroacetic acid	2.2	0	6	0	0	0	5	3	5	10	8	22	0	12.5	5	7.5	15	10	10	18	2	10	0	8	10
Urochloralic acid	10	15	34	40	60	80	10	13	15	20	60	4	30	20	20	30	25	15	10	20	0	20	8	37	20
Trichloroethanol	2	1	12	0	2	18	1	4	5	1.5	1	4.5	7	6	2	13	4	3	2	7	5	2	2	0+*	1
Spinal Fluid.—																									
Chloral hydrate	0	0	0	0	0	1	0	0+	0	0+	1.5	0+	0	1	0	0+	1	1	1	2	0	0	0	0+	0
Trichloroacetic acid	0	0	0	0	0	1	0	0+	0	0	0	0+	0	0	0	0+	0.5	0.5	1	1	0	0	0	0	0
Urochloralic acid	1	2	25	13	16	22	0	0+	10	1	10	5	1	3	1	0	3	6	1.5	7	1	1	1	1	3
Trichloroethanol	0+	1.5	3	0	1.5	1	0	4	5	1	0	2.5	0+	2.5	0+	2.5	2	1	0+	4	0+	0+	0+	3	0.5

*0+ = trace.

either chloral hydrate or trichloroacetic acid. It is a matter of conjecture whether trichloroethanol passes into the cerebrospinal fluid as a free substance or is formed by hydrolysis from urochloralic acid.

Results are expressed in micrograms per milliliter.

Chloral Hydrate.—In one case, there was none in either blood or cerebrospinal fluids; in all other cases, the blood level was considerably higher than the cerebrospinal fluid level. The mean blood level was 10.9; the mean cerebrospinal fluid level was 0.3, or only one thirty-sixth as high. The blood level ranged from 0 to 30 and half the subjects had a value of 10 or more; the cerebrospinal fluid level in every case was 2 or less and about three-fourths of the subjects showed either none or a barely discernible trace.

Trichloroacetic Acid.—In 5 cases, there was none in either blood or cerebrospinal fluid and in one case the cerebrospinal fluid level was slightly higher than the blood level; in all other cases the blood level was higher. The mean blood level was 6.8; the mean cerebrospinal fluid level was 0.2, or only one thirty-fourth as high. The blood level ranged from 0 to 22 and half the subjects had a value of 6 or more; the cerebrospinal fluid level in every case was 1 or less and four-fifths of the subjects had either none or a barely discernible trace.

Urochloralic Acid.—In 2 cases, the cerebrospinal fluid level exceeded the blood level by 1 mg.; in all other cases the blood level was substantially higher. The level in both blood and cerebrospinal fluid was higher than for the other three compounds. The mean blood level was 24.6; the mean cerebrospinal fluid level was 5.3, or about one-fifth as high. The blood level ranged from 0 to as high as 80 and half the subjects had a value of 20 or more; the cerebrospinal fluid level ranged from 0 to 25. Only about one-sixth of the subjects had no urochloralic acid in the cerebrospinal fluid, but half had a value of only 2 or less.

Trichloroethanol.—In 2 cases, the cerebrospinal fluid level was slightly greater than the blood level; in 2 cases, they were equal; in one case there was none in either blood or cerebrospinal fluid. In all other subjects, the blood level was higher than the cerebrospinal fluid level. The mean blood level was 4.2; the mean cerebrospinal fluid level was 1.4, or one-third as high. The blood level ranged from 0 to 18 but half the subjects had a value of only 2 or less; the cerebrospinal fluid level ranged from 0 to 5 but half the subjects had a value of 1 or less and two-fifths had either none or only a barely discernible trace.

Statistical Analysis of the Study of All Four Compounds.—In no case was the cerebrospinal fluid level as high as the blood level and most of the differences were appreciable. The mean blood level was 46.5 while the mean cerebrospinal fluid level was only 7.2, about one-sixth as high. In every case, some measurable level was found in the blood. Values ranged from 10 to 103.5 and half the subjects had values of 50.5 or more. Levels in the cerebrospinal fluid ranged from 0 to 28. Half the subjects had values of 4 or less and 2 subjects had either none or a barely discernible trace.

Comment

The presence of various drugs in the cerebrospinal fluid has been determined. In the noninflamed state the "blood-brain barrier" does not readily permit passage of large amounts of drugs from the blood. Wellman and associates[7] report that the concentration of tetracycline in the cerebrospinal fluid

is one-tenth of that found in the serum. It has been mentioned that the products of internal secretion exercise influence on the permeability of the blood-fluid barrier. The thyroid and sex glands have an increasing effect.[5]

Lous[4] studied the levels of phenobarbital in the blood serum and cerebrospinal fluid in the treatment of epileptics and found that the concentrations in the cerebrospinal fluid and in ultrafiltrates of serum were about 50 per cent of the serum level.

The distribution of chloral hydrate in the brains of dogs was studied[6] but no mention is made of the concentration in the cerebrospinal fluid.

Summary

Twenty-five unselected puerperal patients were included in this study. The cerebrospinal fluid was obtained by lumbar puncture on the third postpartum day; blood was also obtained from the patient at the same time. The medication was administered in rectal suppositories, 1.2 Gm. Specimens were taken at intervals from 30 minutes following administration of the suppository to 10 hours and 30 minutes.

The amounts of chloral hydrate and trichloroacetic acid in the cerebrospinal fluid were small. Urochloralic acid passes into the cerebrospinal fluid in substantial quantities. Exceptionally large quantities of urochloralic acid were demonstrated in Patients 3 and 6. These patients were suffering from severe pre-eclampsia with evidence of liver damage.

The concentration of trichloroethanol in the cerebrospinal fluid is variable, but in general is less than that of either chloral hydrate or trichloroacetic acid.

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FAILURE OF SILVER NITRATE PROPHYLAXIS FOR GONOCOCCAL OPHTHALMIA NEONATORUM

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A VARIABLE small percentage of failure has been reported with the use of silver nitrate in the eyes of the newborn infant in an attempt to prevent gonococcal ophthalmia. A summary of some of these results is given in Table I. It is seen that a fractional percentage of infants acquire the infection despite chemical prophylaxis. Several explanations are offered: (a) the chemical is of little or no value under any circumstance, (b) the drug is not actually placed in contact with the eye, (c) infection is introduced into the eye from the surrounding skin or elsewhere after the drug is given and has been dissipated, (d) no drug was used. Occasional failure to use the drug even though its use is mandatory happens with unknown frequency. This cannot account for most of the cases of unsuccessful prophylaxis. The merits of these arguments have been amply discussed elsewhere,[6, 8, 9] mostly in connection with the relative values of $AgNO_3$ and penicillin. In 1946 we became concerned with an unusually high prevalence of gonococcal eye infections on our newborn service. During the subsequent decade the problem has been under continuous scrutiny. Certain observations made in this connection in a large general hospital will be reported here.

TABLE I. FAILURE OF $AgNO_3$ PROPHYLAXIS FOR GONOCOCCAL OPHTHALMIA NEONATORUM REPORTED IN SEVERAL SERIES

AUTHOR	LOCATION	YEAR	NO. INFANTS	NO. INFECTED
Dieckmann[1]	Jersey City, N. J.	1930-1952	150,000	38
	----------	1948-1953	28,000	1
	----------	1931-1953	70,000	0
	Memphis, Tenn.	1945-1946	4,600	11
	Washington, D. C.	1948-1952	8,000	16
Allen and Barrere[2]	Philadelphia, Pa.	------	1,400	5
Watts and Gleich[3]	New York	1943-1947	11,000	28
Somerville-Large[4]	Dublin, Ireland	1936-1937	2,700	2
Lehrfeld[5]	Philadelphia, Pa.	------	27,900	180
Wolffram[6]	Germany	1945-1947	86,000	82
Wachter and Pennoyer[7]	St. Louis, Mo.	1953-1954	5,500	0

Material

During the ten-year interval, 1946-1956, there were 67,200 live births (excluding sections). Silver nitrate 1 per cent drops were used routinely in the eyes before the infants left the delivery room. A resident, intern, or medical student held the eyelids apart while a nurse put in the drops. Gonococcal

ophthalmia developed in one infant who received prophylaxis under the supervision of a resident to demonstrate to some medical students a proper method to use.

In the above period of time 40 instances of gonococcal ophthalmia occurred. From zero to 8 cases were seen annually. Records of the mothers and infants involved were reviewed in an effort to discover any factors which might have contributed to the contraction of the infection by the infants. The maternal data were as follows: age (16-39 years), parity (32 per cent primiparous), mechanism of delivery (75 per cent normal spontaneous), condition of fetal membranes (intact in 25 per cent of primiparas and 37 per cent of multiparas; 33 per cent of total spontaneously ruptured before labor). The records for the infants showed that 42 per cent were premature (about 10 per cent of all births were premature) and 40 per cent had bilateral involvement. The use of lid retractors during the administration of the $AgNO_3$ did not seem to be a factor that influenced the success of the procedure in preventing infection.

The numbers of infants who developed signs of infection on each postnatal day were as follows: 2 at birth, 9 on the second, 14 on the third, 11 on the fourth, 3 on the fifth, and 1 on the seventh. One full-term infant had edematous eyelids and a hemorrhagic conjunctival exudate noted at birth. Gonococci were seen on smears and recovered in culture. The fetal membranes had been ruptured for 2 days before delivery; the mother was known to have had a purulent vaginal discharge during the week preceding delivery but the exudate was not examined since she did not seek medical care. One premature infant also had a slight conjunctival discharge present at birth and organisms resembling gonococci were seen on smear. The fetal membranes had been ruptured for 24 hours before delivery; there was a normal, spontaneous delivery. The mother was not known to be infected.

Comment

The actual risk during birth of exposure of an infant to gonococci cannot be determined accurately since infected infants are born of mothers who have low-grade infections but who are not known to be diseased and from whom the organism cannot be isolated. One would surmise, however, that the chance of an infant's being infected would be much greater when large numbers of organisms are present in the birth canal as would occur with active infection associated with considerable exudate, or as was the case with one infant in our series, whose mother had had intercourse with the infected father the night preceding delivery of their infant. The variable risk probably associated with the number of organisms in the environment was illustrated by another instance in our series in which only the first of premature twins developed ophthalmia. One might speculate that most of the organisms in the birth canal were removed during the course of delivery of the first of the two infants. In this connection one should note the alleged efficacy of a water flush of the eyes to prevent infection in the newborn.[10] Premature spontaneous rupture of the membranes theoretically might be expected to increase the risk that organisms from the cervix would gain access to the infants' eyes. Wolffram[6] reported that 42 per cent of multiparas and 29 per cent of primiparas who

gave birth to infected infants had prematurely ruptured membranes; the respective figures for mothers of noninfected infants were 13 to 25 per cent for primiparas and 18 per cent for multiparas. Our data cannot be evaluated in this connnection.

Another factor that contributes to the hazard of ophthalmia is prematurity.[6] This presumably is a result of the generally poorer resistance to infection by the immature fetus.

The occurrence of active gonococcal ophthalmia at birth as was noted in 2 instances cited above and as quoted elsewhere[6] demonstrates that postnatal prophylaxis can be futile. Such an event must be extremely rare, however.

Summary and Conclusions

1. Among 67,000 live births during the course of ten years in a large general hospital, 40 infants developed gonococcal ophthalmia neonatorum despite silver nitrate prophylaxis.

2. Prematurity increased the risk of infection.

3. Two infants had active gonococcal ophthalmia at birth.

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A PRELIMINARY REPORT ON CIGARETTE SMOKING AND THE INCIDENCE OF PREMATURITY

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THERE is a difference of opinion among physicians as to the advisability of cigarette smoking during pregnancy. Some physicians believe that smoking has no significant effect on the unborn child; therefore, they do not curtail smoking during pregnancy. Others, who do not feel sure about the prenatal effects of smoking, usually advise their obstetrical patients to cut down on the number of cigarettes per day. Another group of doctors advocate total abstinence, believing cigarette smoking to be harmful to the mother and her unborn child. During the past four decades the incidence of cigarette smoking among women has increased so rapidly as to make this question worthy of a sound scientific answer. Leading obstetricians in the United States and Canada who replied to Campbell's questionnaire reported that 48 per cent of their patients smoked. A search of the literature for a scientific basis on which to advise obstetrical patients in regard to cigarette smoking disclosed that apparently very little research work has been done by way of human experimentation.

Studies of General Interest Concerning the Relationship of Smoking to the Incidence of Physiological Changes in Human Beings.—Bernard[2] made comparative observations in the course of 20 years on 458 women who were habitual smokers and on 5,000 women who did not smoke. He found that disorders of the thyroid were nearly seven times as frequent in smokers as in nonsmokers. Menstrual disorders were present in over 36 per cent of the smokers as compared to slightly over 13 per cent of the nonsmokers. Premature menopause occurred in more than a fifth of the smokers compared with less than 2 per cent of the nonsmokers. Pre-eclampsia was much more frequent in smokers than in nonsmokers. He found that absorption of nicotine, through stimulation of the smooth muscles of the uterus, the tubes, and the ligaments, could lead to contractions of these organs, which he called "genital sensations and tubal cramps."

Roth[3] found that habitual smokers did not show tolerance to certain effects of smoking. The skin temperatures of the extremities decreased; the blood pressure and pulse rate increased, apparently as a consequence of the presence of nicotine. She found that the nicotine in the cigarette must be decreased by more than 60 per cent from that in a standard cigarette before smoking produced only slight or no vascular effects.

Relationship Between Tobacco Plant Employment and the Incidence of Pregnancy Disorders.—Tobacco factories in different parts of the world and

at different periods of time have furnished valuable statistical data on the hazardous effects of contact with tobacco on women and their pregnancies while they are employed in the manufacture of tobacco products. Mgalobeli[4] of Germany reported that among women workers in tobacco factories there were fewer pregnancies, more abortions, and a greater infant mortality rate in the age group from 1 to 3 years. Athayde[5] studied the incidence of abortions and infant mortality in women working in the tobacco industry of Bahia, Brazil. Of 1,866 women capable of procreation, 840 had gestation interrupted by abortion or stillbirth. The percentage of abortions and of stillbirths was more than doubled after they worked with tobacco. Fifteen medical students[6] of the University of Heidelberg investigated the miscarriages among tobacco workers. The statistics of miscarriages varied greatly in different tobacco plants, but the figures for the tobacco industry were significantly higher than those for other industries except the metal industry. However, the metal industry study included only 337 women with 4 miscarriages. This figure constitutes only 5 per cent of the total number of women included in the tobacco industry data. Winkler and Fenner[7] noted a high percentage of delayed menarche, early menopause, menstrual disturbances, dysmenorrhea, and endometritis among women workers in tobacco factories of Germany.

Relationship Between Maternal Cigarette Smoking and Changes in the Fetus.—Human and animal research supports the idea that when cigarettes are smoked during pregnancy the nicotine passes through the placenta to the developing fetus. Sontag and Wallace[8] observed that cigarette smoking during pregnancy increases the human fetal heart rate. This study was carefully investigated by Doerfel[9] who also confirmed the stimulating effect of nicotine on the fetal heart rate by conducting 21 human experiments.

Vara and Kinnunen[10] found that when nicotine was injected into rabbits, changes in the fetus were very strongly histolytic, the nuclei pyknotic and karyorrhectic. They state:

"It thus seems that nicotine passes especially readily through the placenta and destroys the tissues of the fetus during the actively dividing phase in the same way as it affects the germinal epithelium of the ovaries."

Relationship Between Cigarette Smoking and Lactation.—Thompson[11] and later Perlman and associates[12] demonstrated that nicotine is secreted in the breast milk of smoking women. Wilson[13] studied the effect of nicotine on lactation in mice, Hatcher and Crosby[14] on cats, and Thienes and co-workers[15] on rats. It was found that nicotine inhibits lactation, reduces litter size, and, according to Thienes, increases the mortality during the nursing period. Wilson reported no remarkable difference in mortality rate during the period of lactation between the controls and the treated mice. Behrend and Thienes[16] showed that young rats developed marked resistance to the convulsive action of nicotine while adults do not. This may explain why Hatcher and Crosby found that massive doses of nicotine inhibit lactation in cats with no toxic symptoms in nursing kittens.

Other Animal Studies Involving Exposure to Nicotine.—Numerous other animal experiments have been reported which might have some bearing on the effects of cigarette smoking on the pregnant woman and her unborn child. Long and Wolff[17] have pointed out, however, that in interpreting animal data one must be careful not to ignore certain basic differences between animal and human subjects, such as, the relative amounts of the dose of nicotine, the mode and rate of administration, nicotine tolerance, and species differences in response to the drug.

Despite the fact that one should exercise caution in generalizing concerning human beings from observations with infrahumans, several other animal studies are of considerable interest and of possible relevance. Essenberg, Schwind, and Patras[18] found that when pregnant rats were subjected to tobacco smoke approximating human smoking of about one pack of cigarettes per day, two-thirds of all the young were underweight. The young from the nicotine-injected mothers were slightly more underweight than those from the mothers exposed to cigarette smoke. The majority of the underweight young were underweight at the time of birth. Both groups were underweight because of absence of the normal body fat. There was no significant effect on skeletal growth—a fact previously observed by Behrend and Thienes.[19] However, Wilson, McNaught, and DeEds[20] showed that the feeding of nicotine-containing diets to rats led to a slightly though definitely shorter body length than was possessed by animals treated comparably except for nicotine. These contradictory findings might be due in part to the method of administration of nicotine and in part to the effects of oral nicotine on the appetite and food consumption.

A similar experiment was made on rabbits by Schoeneck.[21] The offspring of the female rabbits exposed to cigarette smoke were smaller at birth by 17 per cent than were the controls; the stillbirth rate was 10 times as great, and the mortality rate was definitely increased, since only one-third as many offspring of the mothers exposed to cigarette smoke were alive at maturity.

The effect of nicotine on the estrus cycle has been studied by several workers, but with divergent results. Thienes[22] and Behrend and Thienes[19] injected 5 mg. per kilogram of body weight twice daily into rats over a considerable period of time. There was no alteration of the normal estrus cycle.

Several other studies indicate, however, that nicotine may alter the estrus cycle. Unbehaun[23] and Lee[24] injected nicotine into mice. Nakasawa[25] injected nicotine into white rats. In each case there was an interference with the normal estrus cycle.

A similar result was produced by Wilson and DeEds,[26] who observed that rats fed a diet containing .025 per cent of nicotine had a prolonged and irregular estrus cycle. Doubling the percentage of nicotine in the diet stopped the cycle completely. The fact that these rats ate less than the normal amount of food and the fact that an equally severe estrual disturbance was produced by decreasing the intake of an adequate diet suggests the possibility that the results might have been partially due to malnutrition. This assumption agrees

with that of Evans and Bishop[27] who found that a decreased food intake interfered with a normal estrus cycle. Oral ingestion of nicotine in food might bring about gastrointestinal disturbances, one of which could be impaired appetite.

Purpose

It is the purpose of this preliminary study with human subjects to ascertain the nature and degree of relationship between cigarette smoking and the incidence of premature infant births; and at the same time to determine the interrelationship of these factors and other relevant variables such as age, parity, race, and socioeconomic status.

Definitions.—This study defines a premature infant as one weighing 5 pounds, 8 ounces (2,500 grams), or less at birth. Multiple births are excluded from prematures. Light smokers are those who report smoking between one and ten cigarettes per day. Heavy smokers are those who report smoking more than ten cigarettes per day. Parity refers to the number of children to whom this mother has previously given birth. By no prenatal care is meant that the patient had no more than one visit to the doctor before delivery.

Procedure (Field)

Three years ago a questionnaire was formulated to be used on all obstetrical patients who were delivered at the San Bernardino County Hospital. The gathering of data for this study commenced April 1, 1953. One year later two private hospitals joined the study: St. Bernardine's Hospital and the Loma Linda Sanitarium and Hospital. This report, which covers a period of three years for the County Hospital and two years for the private hospitals, includes 7,499 patients. Copies of the questionnaire were kept in the obstetrical department of each hospital. The data were obtained at the time the birth certificate was filled out—approximately twenty-four to forty-eight hours after delivery. Since it was not convenient to question the mothers before delivery, a double check was made to be sure the information was reliable. A shorter survey sheet was filled out by the Public Health Nurse when she made the home follow-up on the premature births.

The information reported in the hospital survey was consistent with that given in the home follow-up survey except for a few cases in which the home follow-up survey picked up histories of prenatal smoking in patients who were reported as nonsmokers on the hospital questionnaire. There were no cases in which the reverse was true. If there were inaccuracies in reporting the number of cigarettes smoked per day, it appears reasonable to believe that they were toward underestimating rather than overestimating the number of cigarettes smoked. In certain cases, feelings of guilt might have been associated with a tendency of mothers to minimize the number of cigarettes smoked.

It is apparent from this study that the County Hospital represents a different population from that of the private hospitals. When the County Hospital was studied by race, an interesting preponderance of Mexican births became apparent. It was found that 50.6 per cent of all babies delivered at the County Hospital were Mexican and 33.3 per cent were white babies, leaving 16.1 per cent of other races such as Negroes and Orientals. Only 22.5 per cent of Mexican mothers reported smoking, and the prematurity rate for all Mexicans was 7.4 per cent. Approximately 47 per cent of all white mothers admitted smoking with a prematurity rate of 9.6 per cent.

In Fig. 1 the prematurity rates by hospitals for smokers and nonsmokers are shown. For the two private hospitals the prematurity rate is approximately twice as high for smokers as for nonsmokers. A statistical analysis indicates that the prematurity rate for smokers is significantly higher than for nonsmokers (Table I). The probability that such an occurrence is due to errors in sampling is exceedingly remote. The chi square test of 50 with 1 degree of freedom indicates a probability of less than .001. The fact that the difference is less between the prematurity rates for smokers and nonsmokers at the County Hospital than it is at the two private hospitals gives further evidence that the County (or charity) institution apparently represents a different population.

The following factors may have contributed to the higher prematurity rate in County Hospital nonsmokers: poor nutrition, the high incidence of unwed mothers (many of whom may have attempted to induce premature births), and lack of prenatal care. Thirteen per cent of all the mothers delivered at the County Hospital were without legal fathers for their babies; while only 1 per cent of the babies delivered in a private hospital were born out of wedlock. In light of these data, it may be hypothesized that many of the unwed mothers did not make a good emotional adjustment to pregnancy.

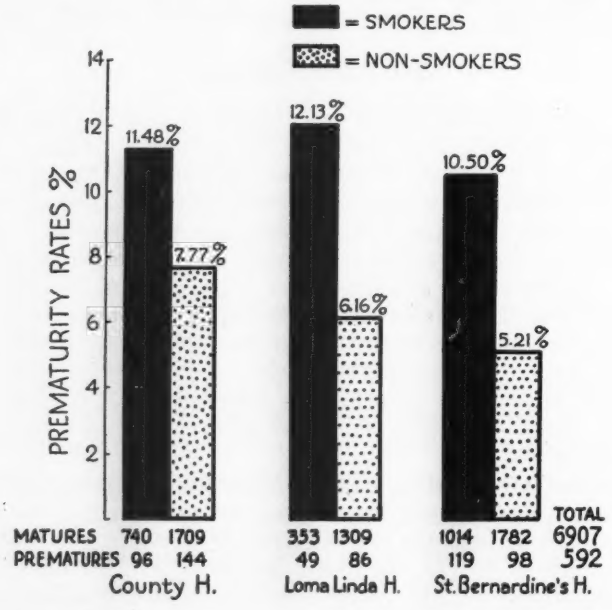
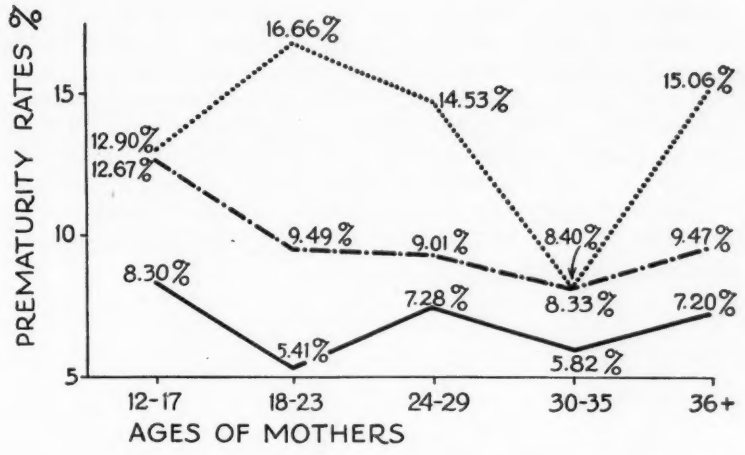


Fig. 1.—Prematurity rates by hospitals for smokers and nonsmokers.

Some of them admitted that they had attempted an abortion. The prematurity rate for unwed mothers at the County Hospital was 10.8 per cent. There was a total of 348 County Hospital unwed mothers, 49 per cent of whom were Mexican, 26 per cent Negro, 23 per cent white, and 2 per cent other ethnic groups. Thirty per cent of County Hospital patients did not receive prenatal care, while only 7 per cent of private hospital patients did not avail themselves of prenatal care.

In Fig. 2 the prematurity rates for heavy smokers, light smokers, and nonsmokers are plotted against the age of the mother. The prematurity rates at every age are consistently higher for heavy and light smokers than for nonsmokers. There is a decrease in prematurity rates for all groups at the age



	Mat.	Prem.	Mat.	Prem.	Mat.	Prem.	Mat.	Prem.	Mat.	Prem.
NON-SMOKERS	298	27	1780	102	1375	108	922	58	425	33
LIGHT SMOKERS	62	9	515	54	434	43	229	21	86	9
HEAVY SMOKERS	27	4	255	51	283	48	154	14	62	11

Fig. 2.—Prematurity rates for nonsmokers, light smokers, and heavy smokers in relation to age of mother.

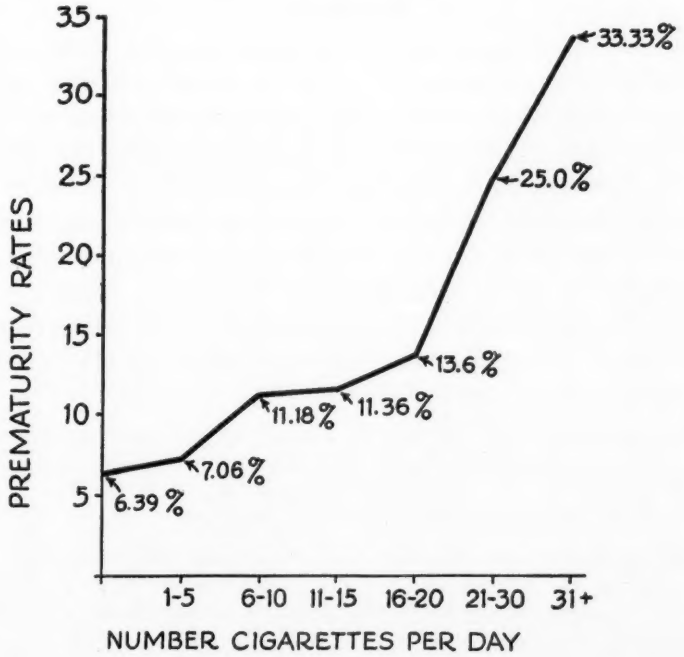


Fig. 3.—Relationship of number of cigarettes smoked per day to prematurity rates.

								TOTAL
Matures	4,800	619	707	242	488	33	18	6,907
Prematures	328	47	89	31	77	11	9	592

of 30 to 35. The reason for this is not at present apparent. For example, from other data analyzed, parity did not appear to be an important factor in prematurity. At least, if parity is a factor, it is masked by other variables.

In Fig. 3 it is apparent that there is a relationship between the incidence of prematurity and the number of cigarettes smoked per day. The more cigarettes smoked each day, the higher is the prematurity rate. The validity of the sudden upswing of the curve is questionable because of the relatively small number of heavy smokers. Additional data for this heavy-smoking range are desirable. When this study has progressed to include a much larger number of premature births, it will be possible to report with greater confidence upon other aspects of this problem.

TABLE I. CALCULATION OF CHI SQUARE

VARIABLE	PREMATURES		MATURES		TOTAL
	ACTUAL NO.	EXPECTED NO.	ACTUAL NO.	EXPECTED NO.	
Smokers	a 264	187.16	b 2107	2183.80	2371 (a + b)
Nonsmokers	c 328	404.80	d 4800	4723.14	5128 (c + d)
Total	592 (a + c)		6907 (b + d)		7499 N

$$X^2 = \frac{(ad - bc)^2 N}{(a+b)(c+d)(a+c)(b+d)} = \frac{(576104)^2 (7499)}{(2371)(5128)(592)(6907)} = \frac{2488886745301184}{49715376456672} = 50.0$$

Summary

This report, which is based upon data gathered from 7,499 patients, shows an incidence of premature births at private hospitals which is approximately twice as great for smoking mothers as it is for nonsmoking mothers. The prematurity rate increases with the number of cigarettes smoked per day. The highest prematurity rates are for heavy smokers and the lowest rates for nonsmokers.

The County Hospital represents a different population in which socioeconomic factors may affect the picture. The prematurity rate for nonsmokers is relatively higher at the County Hospital than at the private hospitals and there is less difference between the prematurity rate for smokers and nonsmokers. Mexicans delivered at the County Hospital report less smoking than any other ethnic group and show the lowest prematurity rate.

The writer is grateful to Dr. William B. Michael for his expert guidance in tabulating and interpreting the data presented. To the following doctors who critically previewed this report goes a vote of thanks: M. E. Cosand, L. Corsa, Jr., C. H. Thienes, L. H. Lonergan, H. N. Mozar, B. W. Halstead, F. R. Lemon, and W. F. Norwood.

Much credit is due to the following supervisors and their assistants who were responsible for gathering the information for the questionnaires: Mary Hyatt, County Hospital Obstetrical Supervisor; Sister Mary Elaine, St. Bernardine's Hospital Records Librarian; Ruth Wipperman, Loma Linda Sanitarium and Hospital Obstetrical Supervisor.

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FETAL SALVAGE IN ABRUPTIO PLACENTAE*

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PREMATURE separation of the normally implanted placenta because of the fetal hazard is one of the most tragic accidents that can occur to the pregnant woman. With the advent of adequate blood banks, maternal mortality has almost reached the vanishing point. Several recent studies have reported maternal death rates from 0 to 1.86 per cent[1-7] with only the report of Page, King, and Merrill[8] showing a rate of 14.0 per cent. On the other hand, a similar reduction of fetal wastage has not occurred and these same reports give a fetal loss of 30.4 to 53.4 per cent.

The histories of all women with abruptio placentae and fetuses that weighed 1,000 grams or more at Research and Educational Hospitals during the period July 1, 1925, to Dec. 31, 1954, were reviewed. Fetal salvage, by birth weight and by severity of the disease, was correlated with the type of therapy.

Many classifications of degree of placenta separation have been proposed, most of them based on postpartum study of the placenta. It seems that a clinical grading of the process might improve management; therefore the classification advocated by Page, King, and Merrill[8] was adopted. As this classification appeared only recently, it is quoted in full:

"Grade 0. These are clinically unrecognized before delivery (diagnosis based upon examination of the placenta).

"Grade 1. These show external bleeding only, or mild uterine tetany, but no evidence of maternal shock.

"Grade 2. In this group there is uterine tetany, ordinarily with uterine tenderness, fetal distress (or death), but no evidence of maternal shock.

"Grade 3. Here there is evidence of maternal shock or coagulation defect, uterine tetany, and intrauterine death of the fetus."

However, several of our patients with severe shock and one with defibrination of blood were delivered of live babies, and were placed in Grade 3, even though intrauterine death of the fetus had not occurred, and it is suggested that Page's classification be modified accordingly.

For the purposes of this study, shock is defined as a drop of 30 mm. in systolic or 20 mm. in diastolic blood pressure, tachycardia of at least 120, with clinical manifestations including clamminess, depressed temperature, air hunger, and sweating.

The definition of toxemia of pregnancy is that proposed by The American Committee on Maternal Welfare.

*Presented at a meeting of the Chicago Gynecological Society, Jan. 20, 1956.

During this thirty-year period, 254 women with premature separation of the normally implanted placenta gave birth to 258 infants who weighed 1,000 grams or more, there being 4 sets of twins. In this same time, there were 26,386 deliveries, giving an incidence of 1:104. Davis[6] reported the incidence of this condition as varying from 1:77 to 1:348. The high incidence in the present series is because of the inclusion of all cases, however mild.

The age of the patients varied from 13 to 45 years, with a mean of 26.1 years and a median of 24.5 years. The parity ranged from 0 to xi, with approximately one-third of the patients nulliparous. The gestational age of the infants was from 6 months to term, the greatest number being at term (Fig. 1).

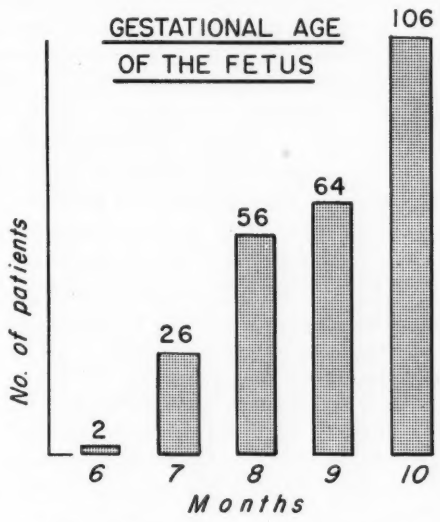

Fig. 1.—Gestational age of the fetus.

There was one maternal death, a mortality rate of 0.39 per cent.

R. T., hospital number 319-890, was a 20-year-old gravida ii, para i. She suffered a mild premature separation of the placenta in the last few weeks of pregnancy and lost about 1,000 c.c. of blood which was replaced by transfusion of a like amount. She gave birth spontaneously to a living 2,800 gram infant. Two months later, she was readmitted to the Medical Service with obvious homologous serum hepatitis. Her condition deteriorated rapidly and she died the day after admission. Autopsy confirmed the diagnosis.

TABLE I. PERINATAL MORTALITY RATE

BIRTH WEIGHT (GRAMS)	NO. OF INFANTS	INFANT DEATHS			INFANT SURVIVAL
		PRIOR TO ADMISSION	BETWEEN ADMISSION AND BIRTH	NEONATAL	
1,000-1,499	32*	7	3	15	7
1,500-2,499	94*†	11	9	13	66
2,500 or more	127*†	12	5	2	108
Total	258	30	17	30	181

*1 set of twins.
†1 of twins.

Two hundred and fifty-eight infants were born of 254 mothers. In 30 instances fetal heart tones were absent on admission to the hospital and 17 additional infants died prior to delivery. Thirty babies did not survive the neonatal period. The uncorrected perinatal mortality rate is 29.84 per cent

(Table I). There was 1 living infant with a tracheo-esophageal fistula and esophageal atresia who subsequently died and one stillborn anencephalic monster.

There was one patient with a coagulation defect. Details of her history are:

H. C., hospital number 423-969, a 27-year-old Negro, gravida ii, para i, appeared for the first time four days before her expected date of confinement, Dec. 18, 1954, with severe pre-eclampsia. She had a blood pressure of 190/112, 2 plus pitting edema, and 2 plus protein in urine obtained by catheterization. There was a living fetus of approximately term size.

Six hours after admission the patient developed severe and persistent abdominal and back pain and passed about 100 c.c. of partially clotted blood vaginally. The uterus was tetanic, but the child was alive with a heart rate of 144 beats a minute. No placental tissue could be felt through the cervcial os. The membranes were ruptured artificially but the vaginal bleeding and abdominal pain continued. Ten minutes later the blood pressure was 110/70 and the fetal heart rate 98.

At this time, the cervix was 6 cm. dilated and nearly effaced, so vaginal delivery was elected. The fetal heart rate continued to grow slower and reached 60 beats a minute. The maternal pulse rose to 112, and the maternal clotting time was 10 minutes.

One hour and twenty-seven minutes after the accident she gave birth spontaneously to a depressed, 2,880 gram infant who survived. Immediately after the birth of the child, the placenta and several large clots were born. In all, she lost about 700 c.c. of blood.

A transfusion was begun but bleeding continued despite oxytocics. No vaginal or uterine tears were found. At this time it was noted that the blood did not clot, and that the patient was bleeding not only from the gums, but also from needle puncture sites. Fibrinogen at this time was later reported to be 100 mg. per 100 c.c. of blood. The patient's pulse was 130 beats a minute and blood pressure 120/90. The uterus was packed to no avail, as she bled through the pack in ten minutes. She was given 2 Gm. of fibrinogen in saline intravenously and bleeding stopped. A total of 2,500 c.c. of blood was given during the entire procedure.

During the puerperium, the blood pressure stabilized at 140/90. The bone marrow was normal and there was no evidence of sickle-cell anemia. The subsequent course was uneventful and the mother and child were discharged in good condition.

Some type of active intervention was done in 153 cases, when maternal or fetal symptoms were of such severity that evacuation of the uterus seemed advisable within a reasonable period of time, usually a maximum of 12 hours. Such intervention varied from simple amniotomy or Pitocin stimulation of labor to cesarean section when apparent or concealed hemorrhage, or fetal distress, made delivery imperative and the vaginal route was not feasible. Cesarean section was done in several instances in the known absence of fetal heart tones because of the severity of the patient's condition. Cesarean hysterectomy was usually performed because of myomas, only 3 instances of uteroplacental apoplexy with failure of uterine contraction being encountered. In the group without active intervention were the patients whose separation was allowed to terminate spontaneously and several who were progressing satisfactorily with no need for interference (Tables II and III).

TABLE II. TIME TO DELIVERY AFTER ONSET OF SYMPTOMS OR ADMISSION TO HOSPITAL

In Labor.—	
Within 12 hours	152
More than 12 hours	51
Unknown	8
Not in Labor.—	
Less than 12 hours	43

The antepartum diagnosis of placental separation was made 173 times, not being suspected in the remaining patients although several had vaginal bleeding or disappearance of the fetal heart tones. Two of these hemorrhages were thought to be due to total placenta previa, the correct diagnosis being made at cesarean section. Using the criteria of Page as modified, there were 81 patients in Grade 0, 96 in Grade 1, 57 in Grade 2, and 20 in Grade 3 (Fig. 2). Fifty-five of these patients had had previous episodes of bleeding in the same pregnancy, none of which were serious and which subsided spontaneously.

TABLE III. METHODS OF MANAGEMENT AND TYPES OF DELIVERY

Spontaneous delivery	173
Amniotomy	86
Cesarean section (9 with hysterectomy)	52
Forceps extraction	22
Breech extraction	12
Pitocin administration	4
Version and extraction	2
Cervical incisions and craniotomy	2
Cervical incisions and forceps extraction	1

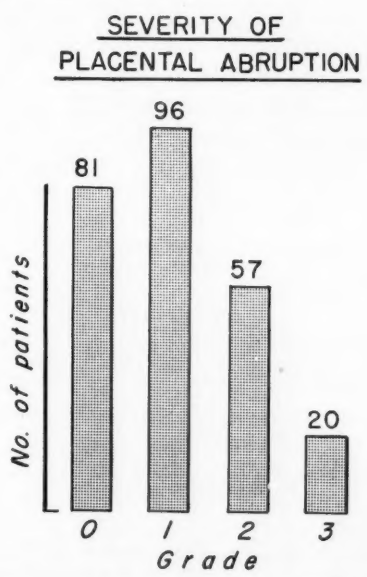

Fig. 2.—Severity of premature separation of the normally implanted placenta.

Forty-two of these women had toxemia of pregnancy, including one with eclampsia, an incidence of 16.5 per cent, which is higher than the 5.5 per cent incidence of toxemia for all patients in this hospital during 1953 and 1954. There was an increase in the number of toxemic patients as the severity of the placental separation increased (Table IV).

TABLE IV. TOXEMIA OF PREGNANCY WITH ABRUPTIO PLACENTAE

GRADE	NO. OF PATIENTS	CASES OF TOXEMIA	APPROXIMATE %
0	81	8	10
1	96	13	14
2	57	13	23
3	20	8	40

Admittedly, there was no chance for fetal survival when heart tones were absent on admission to the hospital. However, when the infants were still living and maternal or fetal symptoms warranted active measures for evacuation of the uterus, fetal survival was 83.5 per cent, while in the passively managed group fetal salvage was 72.8 per cent. Although the numbers are small, this trend continues when fetal size is correlated with survival (Table V). Even in the 1,000 to 1,499 gram group, 6 of 14 infants survived following active intervention, while only one of 11 lived when spontaneous termination of the process was elected.

TABLE V. SURVIVAL OF INFANTS ALIVE ON ADMISSION BY WEIGHT AND TYPE OF THERAPY

BIRTH WEIGHT (GRAMS)	NO. OF INFANTS	ACTIVE THERAPY		PASSIVE THERAPY	
		INFANTS ALIVE ON ADMISSION	INFANTS DIED	INFANTS ALIVE ON ADMISSION	INFANTS DIED
1,000-1,499	32	14	8	11	10
1,500-2,499	99	51	11	37	10
2,500 or more	127	69	3	46	4
		134	16.4%	94	25.5%

On correlation of fetal salvage with the severity of the separation the same trend toward increased infant survival is seen (Table VI). Although separation of Grade 0 severity should be inocuous, by definition, babies were lost and active intervention was usually carried out because of fetal distress, the cause of which was not apparent. Surprisingly, the severe group, Grade 3, where fetal prognosis is nil and where active intervention was carried out in the interest of the mother alone, had a 50 per cent fetal survival rate.

TABLE VI. SURVIVAL OF INFANTS ALIVE ON ADMISSION BY SEVERITY OF SEPARATION AND TYPE OF THERAPY

GRADE	NO. OF PATIENTS	ACTIVE THERAPY		PASSIVE THERAPY	
		INFANTS ALIVE ON ADMISSION	INFANTS DIED	INFANTS ALIVE ON ADMISSION	INFANTS DIED
0	81	20	4	56	16
1	96	67	5	28	5
2	57	34	7	8	4
3	20	12	6	0	0
		133	16.5%	92	27.2%

A few recent reports claim that cesarean section is not indicated for fetal salvage in abruptio placentae, the authors feeling that the survival of infants in distress because of placental separation is not enhanced by abdominal delivery. This has not been confirmed by this study as cesarean section was done not only for severe maternal hemorrhage, but also for early fetal distress when bleeding was in lesser amounts and when immediate vaginal delivery was not possible. There were 46 abdominal deliveries for fetal or combined fetal and maternal indications with 38 living infants (Tables VII and VIII). Two patients with Grade 3 separation of the placenta and with fetal heart tones absent were delivered of living babies by cesarean section done for maternal reasons only and are not included above.

TABLE VII. FETAL SURVIVAL FOLLOWING CESAREAN SECTION BY BIRTH WEIGHT

BIRTH WEIGHT (GRAMS)	INFANTS ALIVE ON ADMISSION	SURVIVED
1,000-1,499	8	5
1,500-2,499	23	14
2,500 or more	15	14

An attempt was made to correlate the estimated amount of placental separation with fetal survival but this was impossible with the information available in the charts.

TABLE VIII. FETAL SURVIVAL FOLLOWING CESAREAN SECTION BY SEVERITY OF PLACENTAL SEPARATION

GRADE	INFANTS ALIVE ON ADMISSION	SURVIVAL
0	4	2
1	15	12
2	19	14
3	8	4

In addition, 2 infants in Grade 3 survived although fetal heart tones were never heard.

Summary

1. Premature separation of the normally implanted placenta occurred 254 times in 26,358 deliveries, an incidence of 1:104, with one maternal death.

2. The uncorrected perinatal mortality rate was 29.84 per cent and there were 2 infants with major congenital abnormalities incompatible with life.

3. The degree of severity of placental separation was classified according to the criteria of Page, as modified, with 81 cases of Grade 0 severity, 96 cases of Grade 1, 57 cases of Grade 2, and 20 of Grade 3.

4. There were 42 cases of toxemia of pregnancy, an incidence of 16.5 per cent, with an increased frequency of toxemia in the severe grades.

5. Some type of active intervention was carried out 153 times with a fetal salvage of 83.5 per cent when fetal heart tones were present on admission to the hospital, while passive management when the fetus was alive resulted in a fetal survival of only 72.8 per cent.

6. Forty-six cesarean sections were done for fetal or combined fetal and maternal indications with an 82.6 per cent fetal survival.

7. There were 3 instances of uteroplacental apoplexy and one of coagulation defect.

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7200 S. EXCHANGE AVENUE

AN EVALUATION OF CONTRACTILE ACTIVITY IN THE LOWER UTERINE SEGMENT IN LABOR BY EXTERNAL TOKODYNAMOMETRY*

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THE basic problem in the assessment of disordered uterine contractility in labor lies in the fact that our understanding of the pattern in normal labor is not yet complete. The activity of the lower segment during labor has not been studied in as much detail as that of the fundus and mid-uterus, and it is the purpose of this investigation partially to close this gap.

In recent years more adequate methods of study have been initiated with the use of such useful apparatus as the multichannel tokodynamometer with strain gage transducers to record uterine contractions and intrauterine pressures,[1] the microballoon electromanometer,[2] and the receptor probe intrauterine recorder.[3] The characteristic features of uterine contractility in the lower uterine segment during labor, such as rhythmicity, intensity, tonus, and distribution of activity, have not previously been amply demonstrated. It is hoped that our presentation will add to a better understanding of the activity of this area in the laboring uterus.

We believe that the major reason for this apparent lack of interest in the physiological activity of the lower uterine segment is based on the general assumption that the changes that occur in it during labor are usually of a passive nature and consist of progressive thinning and some circumferential dilatation. The concept of the passive role of the lower segment has been supported by Reynolds and associates,[4] who expressed the view that there is no essential change in the uterine contractions of the lower segment during the course of labor. They write "In the first stage of labor, 75.5 per cent of primiparous and 93.3 per cent of multiparous women fail to exhibit activity there. In the last two-thirds of the first stage of labor, about 90 per cent of gravidas have inactive lower uterine segments and in those who do exhibit activity, it is inappreciable when compared with the activity of the fundus."

Coordination of action between the upper, middle, and lower segments of the uterus is stressed as a fundamental prerequisite for efficient labor. Reynolds has emphasized the concept that a favorable gradient of uterine activity including fundal dominance is the outstanding feature of good labor. The measurement of this gradient by external tokodynamometric methods is expressed by a formula determined empirically and denotes the total work index in various parts of the uterus during labor. It reflects chiefly the comparative intensities of contractions in a specific uterine locus. The changes

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in intensity in the upper, mid, and lower segments of the uterus, as measured by the external tokodynamometer, bear a direct relationship to the distribution of muscle mass and to the changes in anatomical apposition of the myometrium underlying the recorder. During the phase of cervical effacement, in the first stage of labor there is a redistribution of the myometrium resulting in the formation of the thin lower uterine segment.

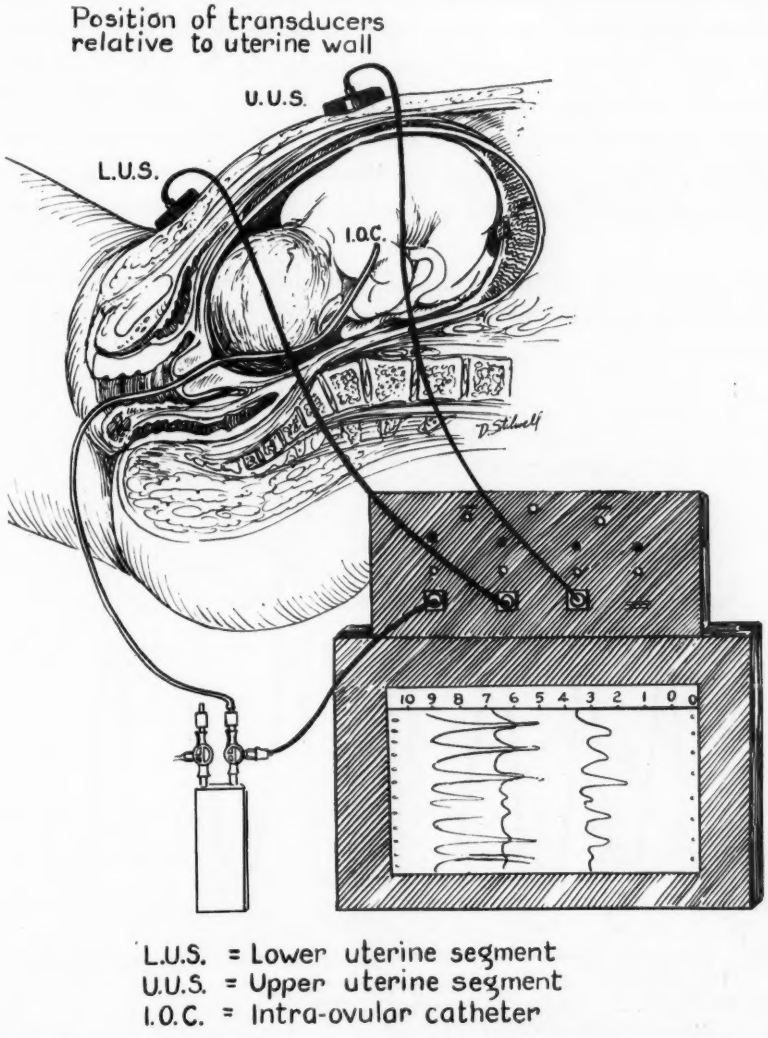

Fig. 1.—Arrangement of tokodynamometer strain gage pressure transducers and P23B pressure transducers.

The tokodynamometer overlying various segments of the uterus is sensitive only to alterations of the surface curvature of the abdomen which are transmitted as pressure changes and recorded as resistance to the flow of an electric current. It is to be expected that the changes in the distribution of the myometrial mass in the formation of the lower uterine segment in normal labor would influence the recordings and alter the intensity. The transmitted

changes in the surface curvature are thus reflected in the calculation of activity gradient. The morphological alterations in the lower segment in the first stage of labor consist of the rearrangement of myometrial mass in this area. The gradient of activity must be influenced by the degree of relative morphological alteration between the fundus and the lower segment which is expressed in terms of intensity by the tokodynamometer. Lower uterine activity can be recorded as long as there is adequate muscle mass beneath the recorder. Activity may be observed in the first stage of labor at the time of the development of the lower uterine segment and thus during cervical effacement. Once cervical effacement is complete, activity in this zone is poorly recorded in some cases because of the marked diminution of the myometrial mass relative to the upper segment. The variability of the thickness of the lower uterine musculature at various stages of labor can be confirmed by direct observation at cesarean section.

The present report is the result of recorded observations in normal labor on the contractile activity of the lower segment compared with that of the upper segment.

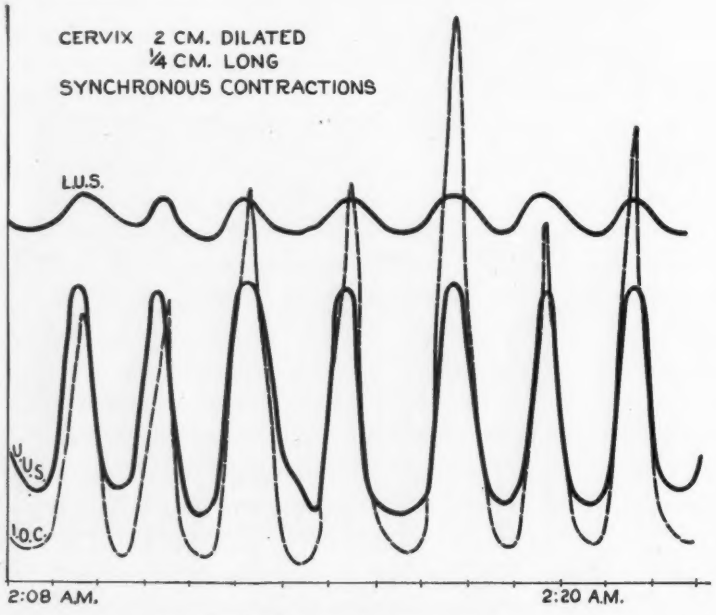

Fig. 2.—Patient C. J. Intensities (average). Group I:
Lower uterine segment—16.2 Gm.
Upper uterine segment—85.1 Gm.
Intraovular catheter—25.0 mm. Hg.
Lower uterine segment activity during effacement.

Material and Method

In this study, 25 unselected cases were observed. The patients were admitted at the thirty-eighth week of gestation (calculated by menstrual dates) for elective induction of labor. Only cases of cephalic presentation were included. Vaginal examination was performed on admission and in each case an estimate was made of the length of the cervix which averaged from 1½

to 2 cm. Care was taken to make sure that the bladder was emptied by preliminary catheterization which was repeated when necessary. A high rupture of the membranes was performed by insertion of a Drew-Smythe catheter through which a polyethylene tube was introduced into the uterus. (The outside diameter of the polyethylene tube was 0.138 cm. and fitted closely to the lumen of the Drew-Smythe catheter.) The polyethylene tube was then attached to a P23B pressure transducer, which in turn was connected to a three-channel tokodynamometer. Two tokodynamometer No. 1 pressure transducers were placed on the abdomen in the following positions: (1) one fingerbreadth above the umbilicus in the midline, (2) immediately above the symphysis pubis in the midline (Fig. 1). Using the method described by Reynolds and associates,[1] continuous recordings were then made from the early first stage of labor through effacement until delivery.

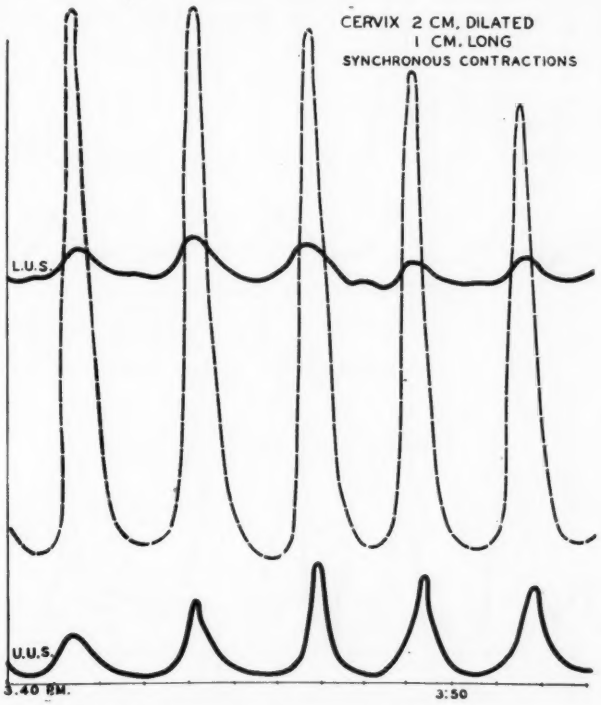

Fig. 3.—Patient C. M. Intensities (average). Group I:
Lower uterine segment—14.8 Gm.
Upper uterine segment—34.4 Gm.
Intraovular catheter—35.2 mm. Hg.
Lower uterine activity during effacement.

Results

Simultaneous intraovular and external tokodynamometer measurements were used to evaluate 25 patients by continuous recording technique. Twenty-three of the patients were multiparas (parity i-iii). There were two primiparas in the series, one of whom had an anencephalic infant. This patient was included in order to determine whether there was any difference in behavior of the lower uterine segment resulting from absence of pressure from the firm fetal head. Her record was like that of the others except that in both primiparas cervical effacement required a longer period. The median duration of labor in the series lay between eight and fifteen hours.

The results of the recordings were divided into four major groups: (I) lower uterine activity during effacement; (IIA) transition from lower uterine activity during the process of effacement to apparent inactivity when full effacement was reached; (IIB) continued lower uterine activity after full effacement; (III) reappearance of lower uterine activity at the end of the first stage of labor; (IV) apparent lower segment dominance during labor.

Group I. Lower Uterine Activity During Effacement.—Recordings obtained during the early first stage of labor showed definite lower uterine segment activity in 22 of 25 patients. The contractions were regular in frequency, intensity, and tonus. Their intensity was less than that observed in the fundus. There was synchronous occurrence of the peaks in the contractions of the fundus and the lower segment. These in turn were synchronous with the maximum recorded intraovular pressure. All 22 of the patients placed in this group showed lower segment activity for a minimum of an hour by continuous recording. The number of contractions varied from 9 to 16 per hour (Figs. 2, 3, 4).

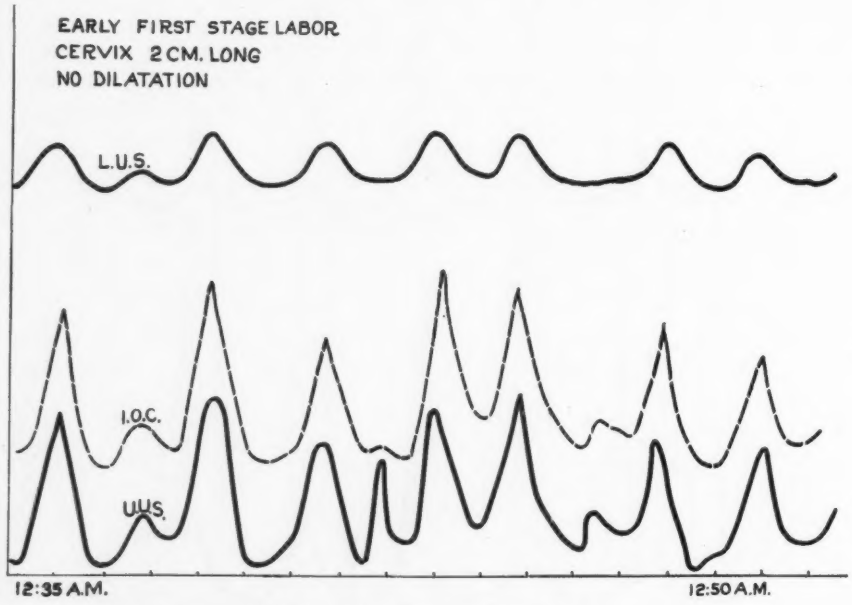

Fig. 4—Patient S. B. Intensities (average). Group I:
Lower uterine segment—18.2 Gm.
Upper uterine segment—51.0 Gm.
Intraovular catheter—9.0 mm. Hg.
Lower uterine segment activity during effacement.

Group IIA. Transition From Lower Uterine Activity During Effacement to Apparent Inactivity When Full Effacement Was Reached.—In 20 of 25 patients we noted a phase of complete inactivity of the lower segment as soon as the cervix became fully effaced. This was brought about by a progressive diminution in the intensity of the contractions of the lower uterine segment, culminating in their absence. The period of transition from full lower segment contractile activity to its disappearance took from twenty minutes to two hours (Figs. 5, 6, 7).

Group IIB. Continued Lower Uterine Activity With Full Effacement.—Despite the clinical status of full cervical effacement, 5 patients did not show the loss of lower segment activity referred to in Group IIA. Rhythmicity,

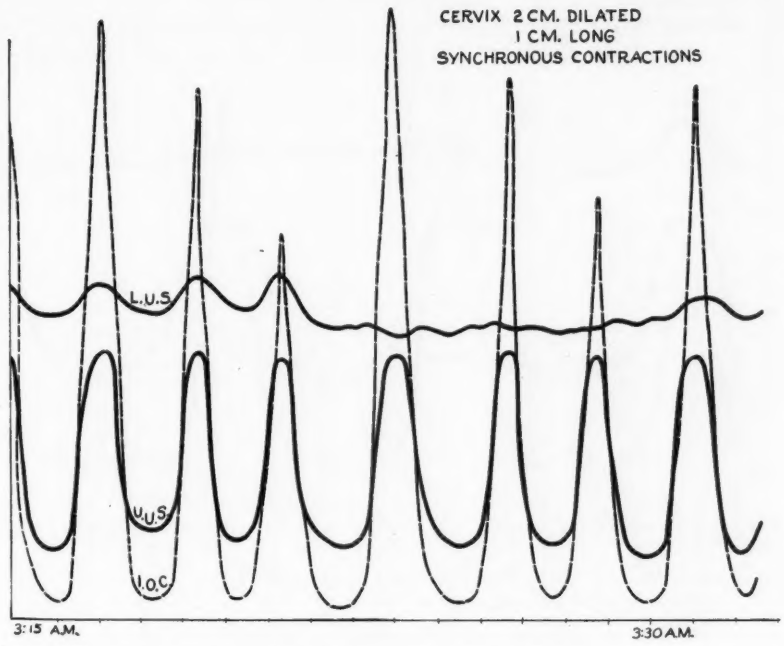

Fig. 5.—Patient C. J. Intensities (average). Group IIA:
Lower uterine segment—7.4 Gm.
Upper uterine segment—87.2 Gm.
Intraovular catheter—34.0 mm. Hg.
Disappearance of lower uterine activity during effacement.

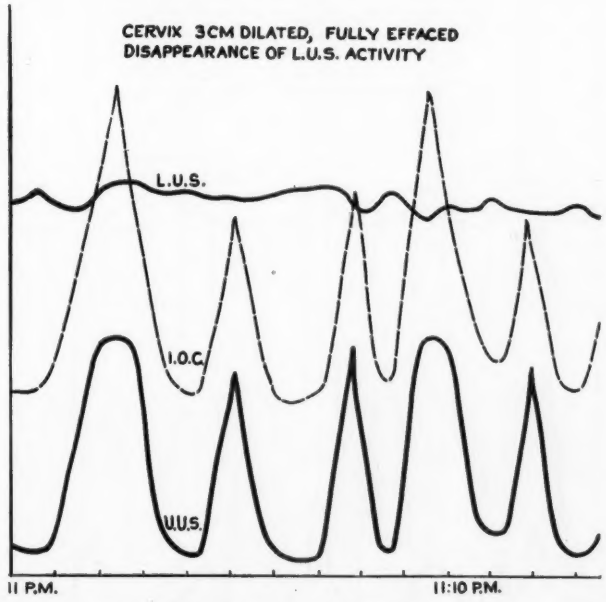

Fig. 6.—Patient S. B. Intensities (average). Group IIA:
Lower uterine segment—3.2 Gm.
Upper uterine segment—88.6 Gm.
Intraovular catheter—14.2 mm. Hg.

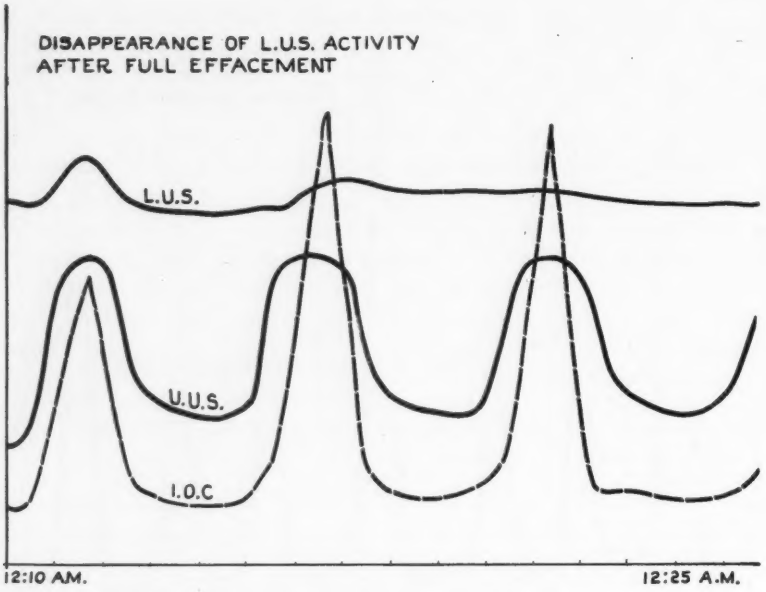

Fig. 7.—Patient A. P. Intensities (average). Group IIA:
Lower uterine segment—14.0 Gm.
Upper uterine segment 71.0 Gm.
Intraovular catheter—31.0 mm. Hg.

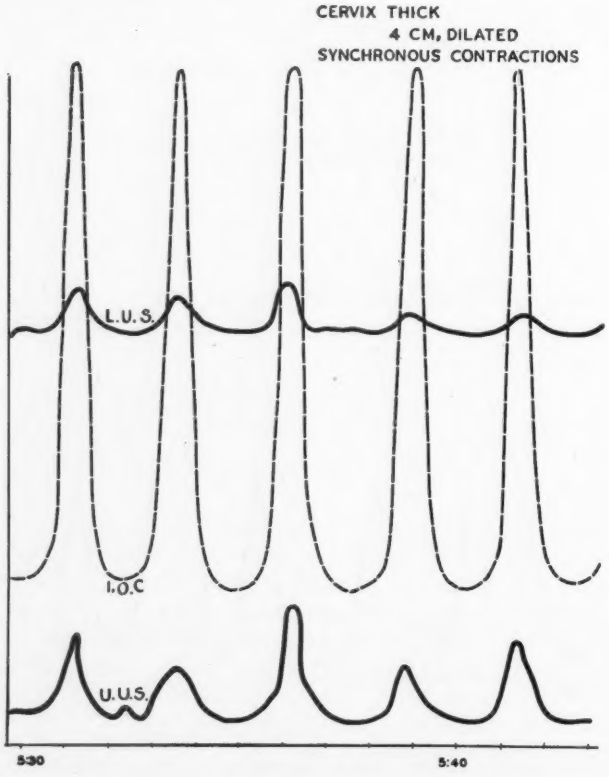

Fig. 8.—Patient C. M. Intensities (average). Group IIB:
Lower uterine segment—16.0 Gm.
Upper uterine segment—34.4 Gm.
Intraovular catheter—36.4 mm. Hg.
Lower uterine activity continued with full effacement.

intensity, and tonus of the lower uterine contractions remained unchanged during early cervical dilatation, diminishing in intensity only late in the first stage. This pattern could be observed for several hours (Figs. 8, 9, 10).

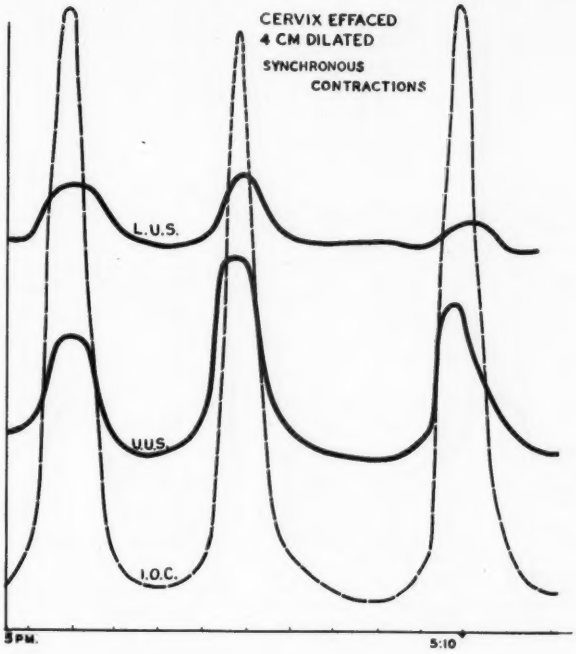

Fig. 9.—Patient D. F. Intensities (average). Group IIB:
Lower uterine segment—21.2 Gm.
Upper uterine segment—64.8 Gm.
Intraovular catheter—42.1 mm. Hg.
Lower uterine activity continued with full effacement.

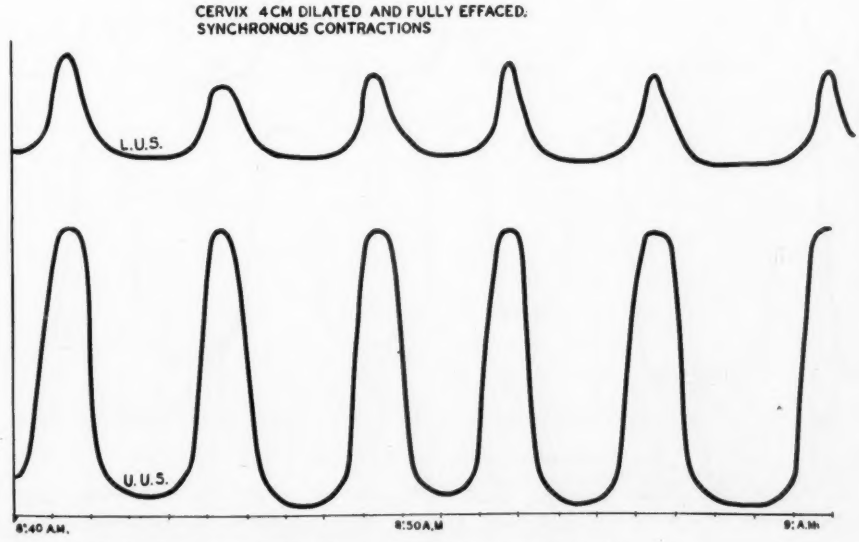

Fig. 10.—Patient C. R. Intensities (average). Group IIB:
Lower uterine segment—36.5 Gm.
Upper uterine segment—130.0 Gm.
Lower uterine segment activity continued with full effacement.

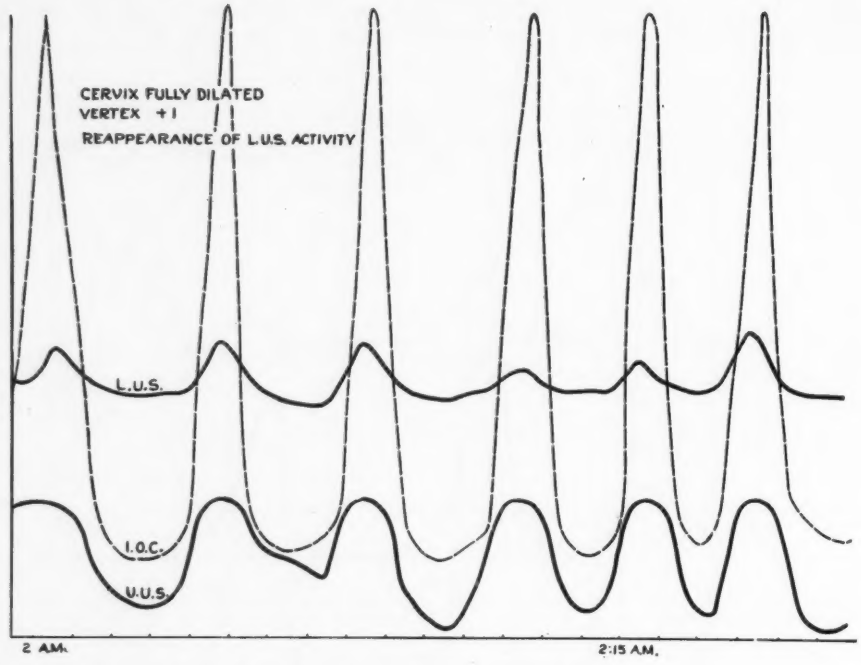

Fig. 11.—Patient S. B. Intensities (average). Group III:
Lower uterine segment—31.2 Gm.
Upper uterine segment—46.7 Gm.
Intraovular catheter—41.5 mm. Hg.

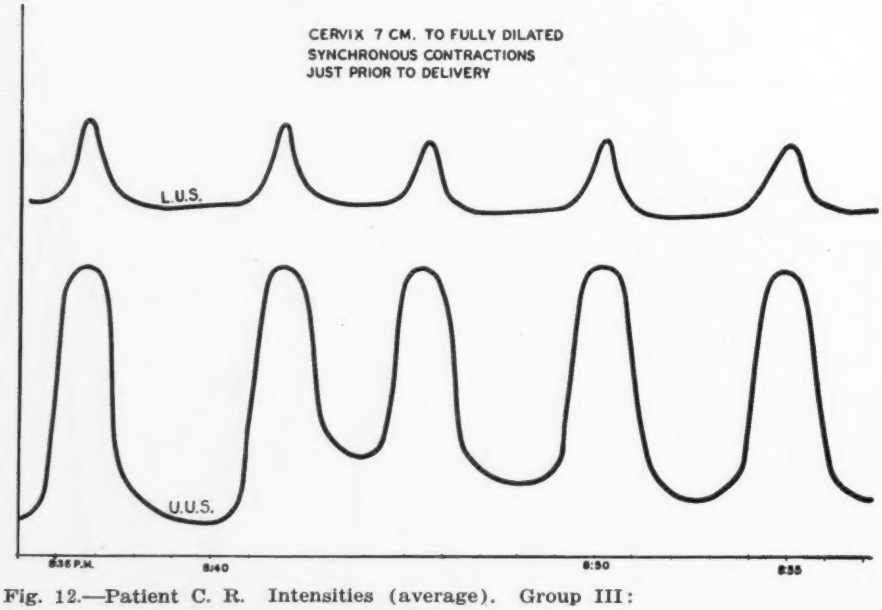

Fig. 12.—Patient C. R. Intensities (average). Group III:
Lower uterine segment—36.5 Gm.
Upper uterine segment 113.6 Gm.
Reappearance of lower uterine segment activity toward the end of the first stage of labor.

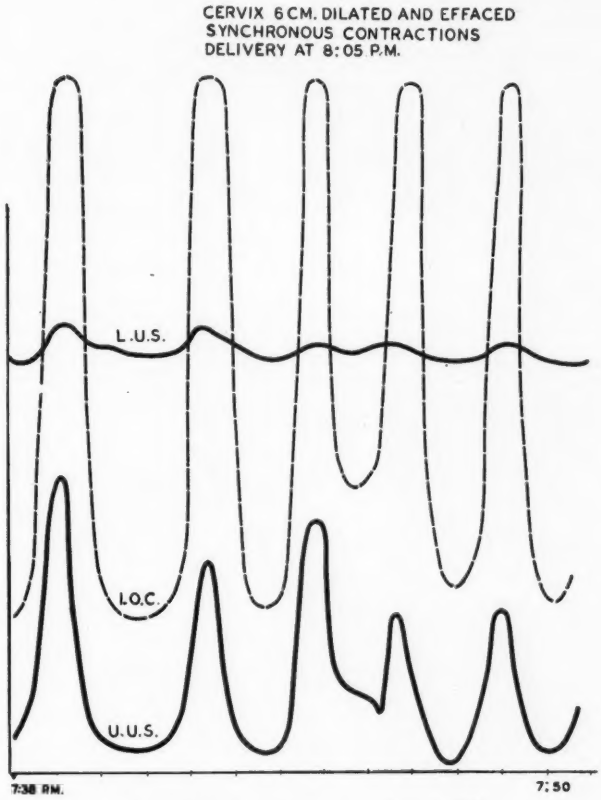

Fig. 13.—Patient C. M. Intensities (average). Group III:
Lower uterine segment 9.0 Gm.
Upper uterine segment—88.0 Gm.
Intraovular catheter—39.5 mm. Hg.
Reappearance of lower uterine segment activity toward the end of the first stage of labor.

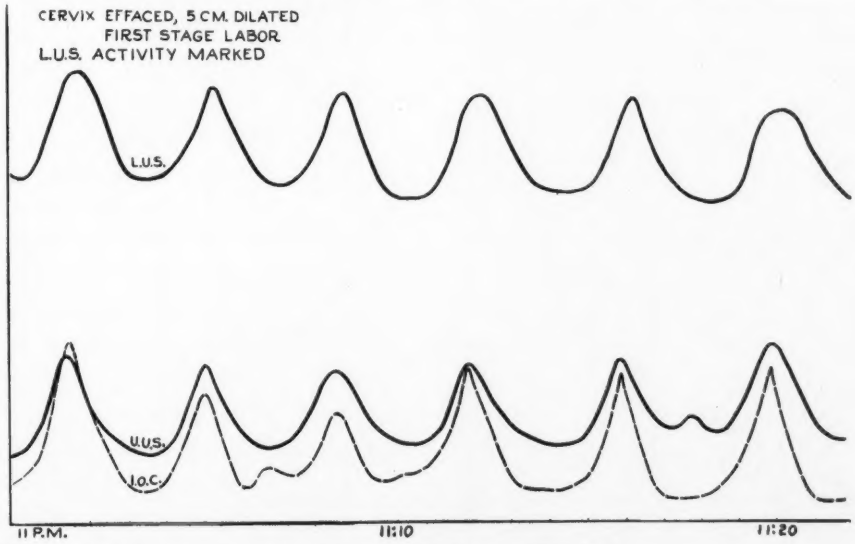

Fig. 14.—Patient A. P. Intensities (average). Group IV:
Lower uterine segment—48.4 Gm.
Upper uterine segment—44.0 Gm.
Apparent lower uterine segment dominance in normal progressive labor.

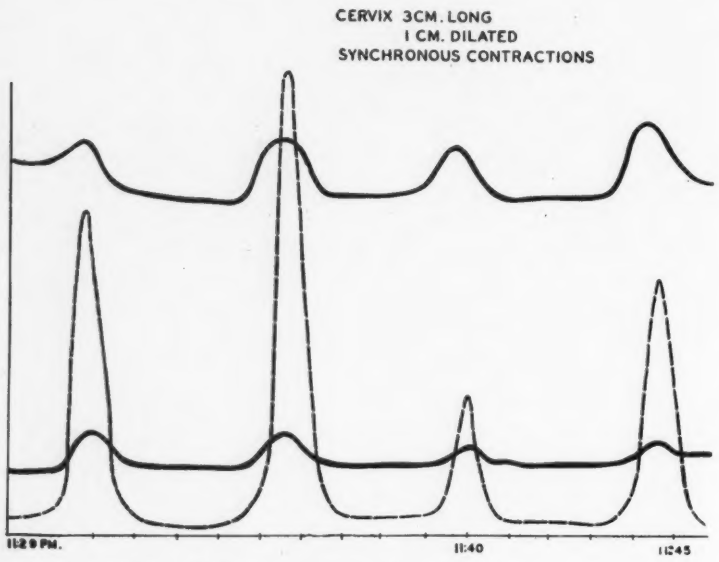

Fig. 15.—Patient I. R. Intensities (average). Group IV:
Lower uterine segment 29.5 Gm.
Upper uterine segment—16.5 Gm.
Intraovular catheter—20.2 mm. Hg.
Apparent lower uterine segment dominance during effacement.

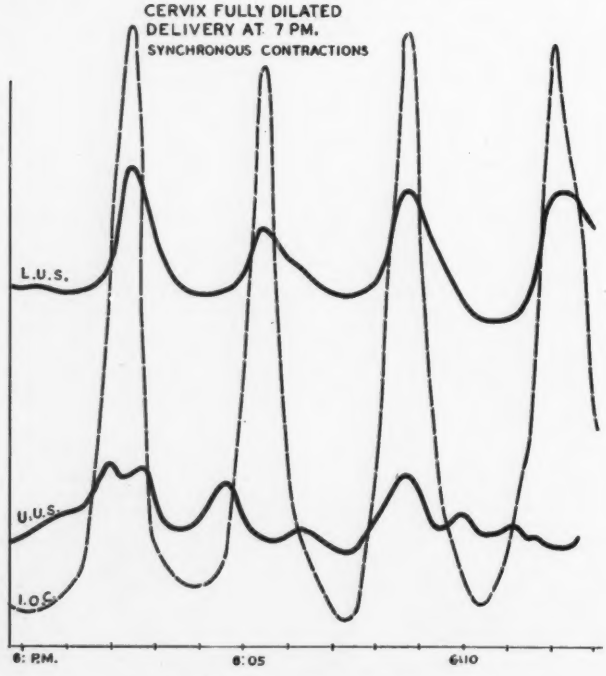

Fig. 16.—Patient D. F. Intensities (average). Group IV:
Lower uterine segment—45.0 Gm.
Upper uterine segment—26.4 Gm.
Intraovular catheter—39.0 mm. Hg.
Apparent lower uterine segment dominance just prior to delivery.

Group III. Reappearance of Lower Uterine Activity at the End of the First Stage.—Moderate to strong lower uterine contractile activity was noted to reappear during the late first stage of labor in 12 of 25 patients. This reappearance of lower segment activity occurred late in labor and was continuously observed until the patient was taken to the delivery room. This activity could be recorded for a period of thirty to forty-five minutes (Figs. 11, 12, 13).

Group IV. Apparent Lower Segment Dominance During Normal Labor.—We are unable to explain transient lower segment intensities noted in all stages of labor which at times were greater than those simultaneously recorded in the fundus. In most patients this phenomenon was observed to last from twenty to forty minutes. In one patient, however, definite lower segment dominance (as illustrated in Fig. 14) was noted throughout the whole of a rapid multiparous labor lasting three hours. Despite the apparent dominance of the lower uterine segment, the normal progress of labor did not appear to be interfered with. This contractility pattern bears a marked similarity to those noted by Karlson[3] which he describes as "a new type of coordination, appearing in the lower segment" (Figs. 14, 15, 16).

Comment

Our data on the behavior of the lower uterine segment in normal labor show it to be more variable than had been suggested by previous observations with the Reynolds tokodynamometer. The activity of this area was demonstrated during labor in the majority of cases in Groups I, IIB, III, and IV. On the basis of these observations, we are inclined to question the passive role previously assigned to the lower segment.

Contractile muscle mass is present in the lower portion of the uterus in the first stage of labor until the redistribution of myometrium results in the formation of the lower uterine segment—that is, in the zone of myometrium bounded superiorly by the physiological retraction ring and inferiorly by the obstetrical internal os. It has been assumed that the recording of such contractility is quantitatively proportional to the amount of active uterine musculature at this location. It is to be expected, therefore, that, as further retraction occurs during cervical effacement, the recordable activity from the lower segment would diminish and gradually disappear. The phenomenon is substantiated by the clinical correlation of the recordings in Group IIA with the degree of cervical effacement.

The variability in the physiological behavior of the uterus is expressed in the numerically smaller Group IIB, in which continued lower uterine activity is recorded without significant alteration of intensity when full cervical effacement is reached, and one assumes the lower uterine segment has been well formed. This suggests that there is an individual variation in the degree of redistribution of myometrial mass. This may be verified by direct clinical observations at cesarean section performed after full cervical effacement has occurred. In some patients we find the lower segment thin and well defined while in others it is still thick and incompletely formed. In order to demonstrate these normal differences in contractile behavior, it is essential that continuous recordings be made throughout the entire course of labor.

It is postulated that in some cases the part played by the lower uterine segment is an active one during labor. It is this activity which may play an important etiological role in the rupture of uteri previously weakened by known or unknown anatomical or pathological causes.

Reynolds and associates[1] have considered labor to be established only when the cervix is dilated 2 to 3 or more centimeters, a definition to which we cannot subscribe. According to both our clinical experience and experience with the tokodynamometer, labor begins with regular, rhythmic contractions which effect cervical effacement. By the time the cervix begins to dilate, labor has not only begun but is well established. Reynolds concluded that prior to labor 80 per cent of women show lower segment activity and the "development of inactivity in this region during labor is one of the cardinal signs of fundal dominance and good labor." It should be further emphasized, in view of our findings, that fundal dominance is probably an effect of myometrial redistribution in the formation of the lower segment as recorded by external tokodynamometry. The lower segment activity recorded "prior to labor" by Reynolds correlates with Group I during cervical effacement.

Analysis of the recordings in Group III shows a somewhat surprising reappearance, in a number of cases, of moderate to strong activity when full dilatation has occurred, just prior to the expulsive phase. How can this activity be explained on physiological or anatomical grounds? Lower segment activity at full dilatation probably results from the function of the circular muscles of the lower segment which apparently play a part in expulsion.[11] Perhaps the answer may lie in exact knowledge of the function and histology of the fully dilated human cervix. The relative amounts of muscle elements in the cervix at this stage and their function remain controversial. Much work has been done in investigating the possible contractile function of cervical musculature.

Nixon,[5] Hughesdon,[6] Wendell-Smith,[7] and Danforth[8] have studied cervical musculature and its activity. Danforth's studies on pregnant and nonpregnant uteri show that the human cervix is predominantly a fibrous connective tissue structure with so-called muscular elements consisting of isolated strands of smooth muscle. He also has shown that isolated strips of tissue taken from the pregnant human cervix at two months' gestation are capable of some contractile activity, which is negligible when compared with that of the corpus. He states that "the average total amount of smooth muscle in the human cervix approximates 10 or 15 per cent; in the occasional case the smooth muscle content in the human cervix may be as high as 40 or 45 per cent." He also states that the muscular tissue is capable of contracting. It is perhaps this anatomical variation in muscle mass which accounts for the reappearance of contractile activity in the cases presented.

Hughesdon, describing the anatomy of the human cervix in pregnancy, states that "during pregnancy collagen fibers are progressively reabsorbed and

replaced by fluid. Towards term the cervix consists of a central mass of non-contractile tissue—immature muscle, collagen, and fluid—with mature muscle layers, transmitting the pull of the upper segment, applied tangentially across the top and down the side."

Dr. Nixon, using intracervical and intrauterine balloons, has shown that the human cervix is capable of greater contractions than the fundus following the injection of ergometrine. The contractions "did not occur at the same time as those of the corpus."

It becomes evident from a survey of these observations on the contractility of the human cervix, that a much more complete study of its action is necessary.

Alvarez and Caldeyro-Barcia[2] demonstrated lower uterine activity in normal[9] and in prolonged labor. Activity in the lower segment in cases of prolonged labor appeared to be of greater intensity than that of the fundal contractions. These workers have also shown ascendant waves presumably arising from the lower segment which occur prior to the contractions in the fundal area. These characteristics are described as consistent with a decrease in the labor efficiency of the contractions. Group IV cases, in the present study, indicate that lower segment intensities can be recorded in normal labor and that in some instances these can be transiently or continually in excess of those of the fundus. Neither the duration of labor nor the progress of effacement and dilatation of the cervix was delayed in our cases. This finding supports those of Halliday and Heyns,[10] who obtained synchronous deflections from the upper and from the lower uterine segments in some cases but not in others. They showed that deflections obtained from the lower uterine segment could be smaller, equal to, or greater than those from the upper uterine segment. This biological variant in activity should be taken into consideration when abnormal or prolonged labor is evaluated.

Summary

1. External tokodynamometric recordings with special reference to the lower uterine segment were made in an unselected consecutive series of 25 patients who were 38 weeks pregnant, 23 of whom had borne one to three children. Labor was initiated by artificial rupture of the membranes. Recordings were started before labor and continued throughout the first stage and into the early second stage, to study the pattern of contractility before and during full development of the lower uterine segment.

2. The patterns recorded included: (I) lower segment activity during effacement; (IIA) transition from lower uterine activity during effacement to apparent inactivity with full effacement, shown in a majority of the group; (IIB) continued lower uterine segment activity after effacement, shown in a minority; (III) reappearance of lower segment activity in the late first stage in 12 patients; (IV) dominance of lower segment activity over fundal activity for a period of twenty minutes to three hours without appreciable change in the character of labor. This was in a small group.

3. It is postulated that these changes reflect myometrial redistribution in labor during the formation of the lower uterine segment and that this factor

should be taken into consideration in the interpretation of uterine physiology as recorded by external tokodynamometer.

4. Continued activity of the lower uterine segment after full effacement may be an important etiological cause for rupture of the lower uterine segment during labor in both the intact uterus and the uterus after previous cesarean section.

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C-REACTIVE PROTEIN IN PREGNANCY*

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HEART disease, it has been estimated, complicates one in every hundred pregnancies and accounts for about 1,000 maternal deaths annually in this country.[1] Since most of these cases are rheumatic heart disease, it is desirable for the obstetrician to have a simple test which will help him to determine rheumatic activity in any given case. While the C-reactive protein test has proved useful for this in nonpregnant patients,[2-5] the findings concerning its possible usefulness in pregnancy are meager and somewhat ambiguous.[2, 6] It was decided, therefore, to do a more extensive study of C-reactive protein in pregnancy and to compare it to the erythrocyte sedimentation rate.

In 1930 Tillett and Francis[7] discovered that an unidentified substance in the sera of patients with pneumonia precipitated when combined with the C fraction polysaccharide of pneumococci. Subsequent work has resulted in the crystallization of this substance,[8] and in the development of a simple test for its presence.[9] Clinical studies have shown that this test is useful in diagnosing and following the clinical progress of acute rheumatic fever, pneumonia, rheumatoid arthritis, acute myocardial infarction, and possibly other inflammatory or degenerative conditions.[2, 4-7, 10]

Materials and Methods

The present study involved a control group of 23 nonpregnant women with no abnormalities and an experimental group of 110 women. The experimental group was subdivided into four smaller groups (see also Table I):

1. A first trimester group of 35 women who were between the first and fourteenth menstrual weeks of pregnancy.
2. A second trimester group of 36 women who were between the fifteenth and twenty-seventh weeks of pregnancy.
3. A third trimester group of 39 women who were between the twenty-eighth and fortieth weeks of pregnancy.
4. A postpartum group of 23 women who were from three hours to one week post partum.

The tests run on these patients were the erythrocyte sedimentation rate and the C-reactive protein test. The sedimentation rate was done according to the method described by Wintrobe,[11] and was corrected for the hematocrit

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**Work carried out in partial fulfillment of the requirements of the Project Teaching Program of the Medical Curriculum, Western Reserve University School of Medicine.

according to the chart published by Wintrobe and Landsberg.[12] The C-reactive protein test was done by the technique described by Anderson and McCarty,[9] using commercially prepared antiserum (Schieffelin).

Results

In compiling the results that are shown in the tables and figures, any sedimentation rate that was 20 mm. per hour or greater was regarded as elevated, as suggested by Wintrobe and Landsberg.[12] None of the subjects in the control group gave positive C-reactive protein responses (Table I). In the pregnant group, however, 19 of the 110 subjects, or 17 per cent, had positive tests. Statistical analysis disclosed two important points: (a) there is a significantly greater incidence of positive responses in the pregnant group than in the control group, and (b) there is no significant difference between the rates of incidence in the various trimester groups within the pregnant group (Fig. 1). The pregnant group can, therefore, regardless of the duration of the pregnancy, be treated as a single population which is significantly different from the control group. Further analysis of the pregnant group shows that the 19 women with positive C-reactive protein tests are in the same

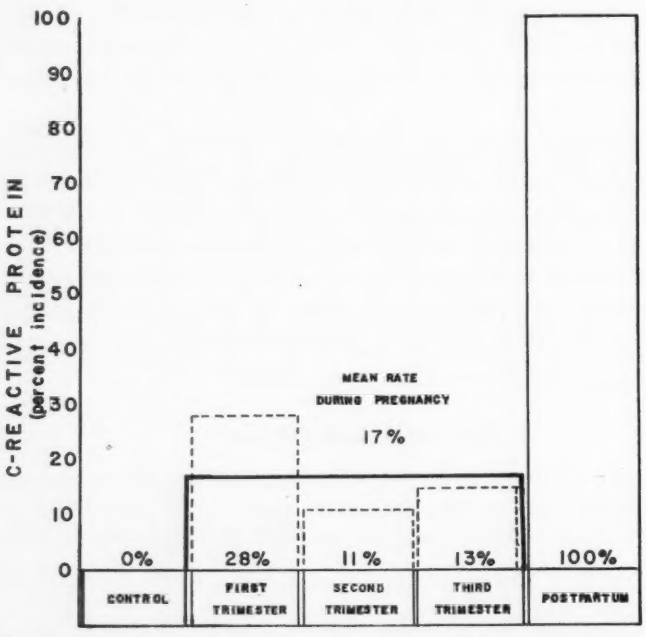

Fig. 1.—The rate of incidence of C-reactive protein through pregnancy and the immediate puerperium. In the nonpregnant control group none of the 23 subjects gave positive C-reactive protein responses. The three trimester groups were made up of 35, 36, and 39 subjects, respectively. Of the 19 pregnant patients giving positive responses, 10 were from the first-trimester group, 4 from the second, and 5 from the third-trimester group. In the postpartum group, all 23 subjects had positive tests.

average age group and the same average parity group as the other 91 women who did not have positive tests. Since this test is nonspecific, being positive in a number of inflammatory or degenerative conditions, the magnitudes of the responses and the clinical findings other than pregnancy should be taken into consideration (Table II). A response of greater than 2 plus was given by only 2 of the 19 patients who had positive C-reactive protein tests; one, a patient suffering from severe acute vaginitis with ulceration, gave a 3 plus response, while the other, a patient with abdominal pregnancy and active cystitis, had

a 4 plus response. In contrast to the control and pregnant groups, the postpartal group had positive C-reactive protein tests in 100 per cent of its 23 subjects.

TABLE I. RESULTS OF C-REACTIVE PROTEIN TESTS AND COMPARISON OF CRP WITH THE CORRECTED WINTROBE ERYTHROCYTE SEDIMENTATION RATE

GROUP	NUMBER IN GROUP	NUMBER IN GROUP WITH HIGH ESR	NEGATIVE CRP		TRACE OF CRP		CRP 1+		CRP 2+		CRP 3+		CRP 4+	
			NO. IN GROUP	NO. WITH HIGH ESR	NO. IN GROUP	NO. WITH HIGH ESR	NO. IN GROUP	NO. WITH HIGH ESR	NO. IN GROUP	NO. WITH HIGH ESR	NO. IN GROUP	NO. WITH HIGH ESR	NO. IN GROUP	NO. WITH HIGH ESR
Control	23	2	23	2	0	0	0	0	0	0	0	0	0	0
First trimester	35	22	25	13	0	0	5	4	3	3	1	1	1	1
Second trimester	36	19	32	17	3	1	1	1	0	0	0	0	0	0
Third trimester	39	31	34	27	1	1	3	2	1	1	0	0	0	0
Post partum	23	21	0	0	2	2	1	1	13	11	4	4	3	3

TABLE II. DETAILED DATA ON PATIENTS WITH A POSITIVE C-REACTIVE PROTEIN TEST DURING PREGNANCY

GROUP AND PATIENT NO.	AGE	PARITY	C-REACTIVE PROTEIN RESPONSE	HEMATOCRIT	CORRECTED ESR	CLINICAL FINDINGS (OTHER THAN PREGNANCY)
First Trimester.—						
67	33	3	2+	37	21	None
74	21	2	1+	34	36	None
82	37	1	1+	44	34	4+ Wassermann
96	23	2	2+	42	43	None
97	30	1	4+	34	40	Active cystitis; abdominal pregnancy
98	32	5	1+	39	43	None
20L	31	2	2+	33	33	Hyperemesis
21L	28	2	1+	44	12	Glomerulonephritis (diagnosis uncertain at time of test)
29L	30	1	1+	32	33	Threatened abortion
31L	20	2	3+	28	31	Severe acute vaginitis with ulceration
Second Trimester.—						
58	26	4	Trace	37	30	None
83	34	2	1+	39	45	Nontoxic goiter (had complete physical)
101	17	0	Trace	24	0	Sickle-cell anemia
102	21	1	Trace	38	18	None
Third Trimester.—						
4	19	1	1+	35	34	None
28	20	1	1+	35	40	None (had complete physical)
33	24	0	1+	38	8	"Sore throat"
44	22	0	2+	34	33	Dental extraction on day before test
34L	19	0	Trace	40	40	Glomerulonephritis

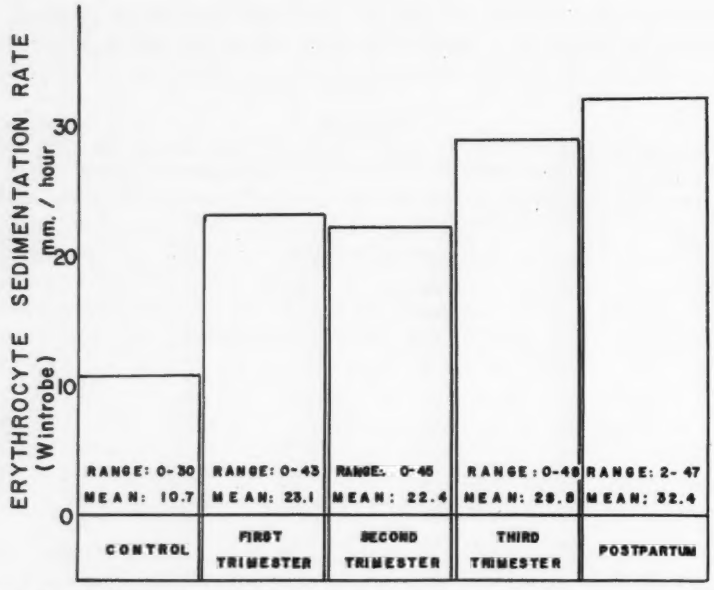

Fig. 2.—The erythrocyte sedimentation rate through pregnancy and the immediate puerperium. In the control group only 2 of the 23 subjects, or 9 per cent, had sedimentation rates over 20 mm. per hour. In the first-trimester group, however, 63 per cent of the 35 patients had elevated sedimentation rates, while in the second-trimester group 53 per cent of the 36 patients had elevated sedimentation rates. It should be pointed out that, while the mean sedimentation rates of these groups is also different, the difference between these means is not statistically significant. In the third-trimester group, 80 per cent of the 39 patients had elevated sedimentation rates. While 91 per cent of the 23 postpartum patients had elevated sedimentation rates and the mean rate for this group was 32.4 m.m. per hour, this rise is not statistically significant as compared to that of the third-trimester group. It is of interest to note that no postpartum drop in sedimentation rate was observed in this study as has been previously reported.[4]

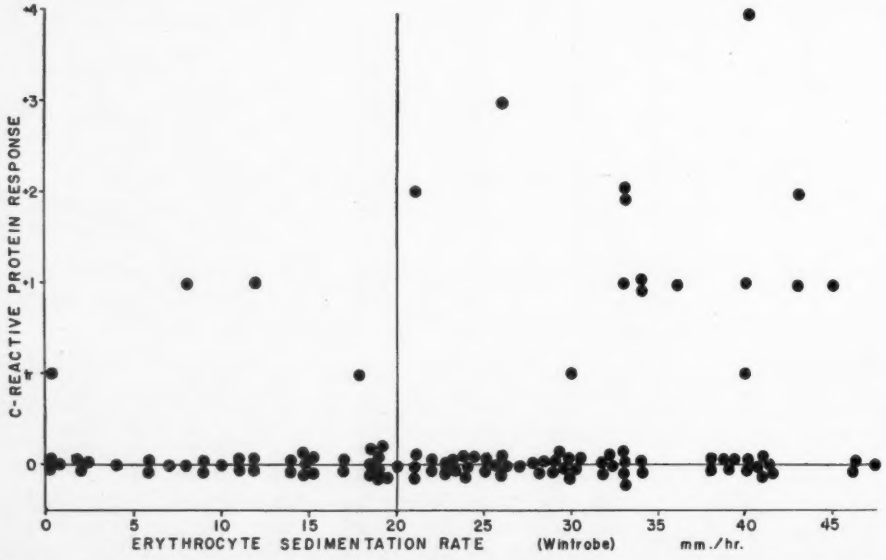

Fig. 3.—Correlation of the C-reactive protein response and the erythrocyte sedimentation rate during pregnancy. Of the 110 pregnant subjects tested, 19 gave positive C-reaction protein responses. Sixty-eight per cent, or 13 of the 19, also had sedimentation rates of 30 mm. per hour or greater, and 74 per cent had sedimentation rates of more than 20 mm. an hour. Although this indicates that a positive C-reactive protein response is associated with a high sedimentation rate, it should be noted that of the 42 patients with sedimentation rates of 30 or more, only 30 per cent had positive C-reactive protein tests, and of the 74 patients with rates of greater than 20 mm. per hour, only 21 per cent gave positive C-reactive protein responses.

The mean erythrocyte sedimentation rate of the control group was 10.7 mm. per hour, and of these only 2, or 9 per cent, were 20 mm. per hour or greater. In the pregnant population, however, the mean sedimentation rates were 23.1, 22.4, and 28.8 mm. per hour for each of the respective trimester groups (Fig. 2). The mean for the postpartal patients was 32.4 mm. per hour. Statistical analysis again shows that the experimental groups are significantly different from the control group. Further analysis, however, shows that the first- and second-trimester groups are not significantly different from each other, but that they are separate from the other groups. The third-trimester and postpartal groups may, likewise, be grouped together into a single population statistically different from the others.

Comment

In previous work on C-reactive protein in pregnancy, Hedlund[2] studied 25 patients in all trimesters of pregnancy and found that none of them gave positive responses. Sheltar and his associates,[6] on the other hand, tested a group of 27 women in the third trimester of pregnancy and found that 10, or 37 per cent of them, gave positive responses. Hedlund, however, used the capsular swelling technique, while Sheltar and his workers used the precipitin test.[9] In the present study, with the use of the precipitin test, the results for the entire period of pregnancy show an incidence of C-reactive protein in 17 per cent of the subjects, while in the third-trimester group the rate was 13 per cent.

The results of this study confirm the finding of previous workers[13, 14] that the sedimentation rate tends to increase as pregnancy progresses. However, no postpartum fall in the sedimentation rate, as reported by Hamilton,[13] was observed in this study. In explanation of the divergence between Hamilton's findings and those reported here, it may be pointed out that Hamilton took her postpartum specimens from patients who were from six to eight weeks post delivery, while in the present study the patients were in the immediate puerperium, ranging from three hours to one week post partum.

In correlation of the C-reactive protein test with the erythrocyte sedimentation rate in pregnant patients (Fig. 3), 68 per cent, or 13 of the 19 patients with positive C-reactive protein tests also had sedimentation rates of 30 mm. per hour or greater, while 74 per cent, or 15 of the 19 had sedimentation rates of 20 mm. per hour or greater. Conversely, however, only 30 per cent, or 13 of the 42 pregnant patients with sedimentation rates of 30 mm. per hour or greater had positive C-reactive protein responses, while only 21 per cent, or 15 of the 73 patients with sedimentation rates greater than 20 mm. per hour had positive C-reactive protein responses. In summary, a pregnant patient with a positive C-reactive protein test will probably have an elevated sedimentation rate, but only a relatively few of the patients with high sedimentation rates will give positive C-reactive protein responses.

Summary and Conclusions

1. C-reactive protein tests and the determination of erythrocyte sedimentation rates were done on 156 female subjects. Of these subjects, 110 were

pregnant, 23 were from three hours to one week post partum, and 23 served as nonpregnant controls.

2. None of the subjects in the nonpregnant group exhibited positive C-reactive protein responses. Seventeen per cent of the pregnant subjects showed positive C-reactive protein responses, while those of the postpartum subjects were positive in every case.

3. Pregnant patients exhibiting positive C-reactive protein responses usually have high sedimentation rates. On the other hand, of all the pregnant patients with high sedimentation rates, relatively few show positive C-reactive protein responses.

We would like to acknowledge the assistance of Dr. Charles H. Hendricks.

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Gynecology

RELATION OF OVARIAN STROMAL HYPERPLASIA TO ENDOMETRIAL CARCINOMA*†

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UNOPPOSED estrogen stimulation has been suggested as an etiological factor in the production of carcinoma of the endometrium. The source of this postulated estrogen in the postmenopausal woman has been the object of investigation by those who support this view. Frequently mentioned is ovarian stromal hyperplasia, an entity which has been reported in a preponderance of women with endometrial cancer. This hyperplasia of stromal cells in the postmenopausal ovary is postulated to be the source of estrogenic hormone and thus to prepare or predispose the individual for endometrial carcinoma.

In 1942 Smith, Johnson, and Hertig[9] discussed ovarian stromal hyperplasia. They noted changes in postmenopausal ovaries which appeared to be frequently associated with hyperplastic bleeding endometria. The main characteristic of these changes was described as the presence of "masses of dense, well vascularized, stromal tissue in either the cortex or the medulla of the ovary with a tendency to form whorls." Some of these cells become large and polyhedral and contain fat, resembling cells of the theca interna. Going farther, they stated that "when large numbers of these cells form a nucleus, there tends to be some infiltration of lymphocytes and macrophages in the area, associated at times with cholesterol-like slits." These structures they called cortical granulomas. They found almost constant association of these lesions with hyperplastic bleeding endometria and suggested a relation between the "cholesterol slits" and estrogen production. In reviewing the ovaries from 180 patients with endometrial carcinoma, they found that 87 per cent showed slight to marked theca-cell activity and that in 77 per cent of 62 cases in which the uninvolved endometrium was available, there was more or less proliferation, mostly less.

In his discussion of the "aging ovary," Hertig[2] mentioned the above work and elaborated further to the effect that the ovarian stromal activity begins to appear at 45 to 49 years of age and is more apparent after 50 years, "especially in those with endometrial activity or outright malignancy." Jones and

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Brewer,[3] however, in studying the endometria and ovaries in 68 women with endometrial carcinoma, found very little evidence of estrogen stimulation in the uninvolved portions of endometrium and described no ovarian changes.

In a long review of the subject, Woll, Hertig, Smith, and Johnson[13] discussed the ovarian stroma in senescence and senility and set down criteria for diagnosing or recognizing ovarian stromal hyperplasia. The important features in normally senescent ovarian stroma as described by these authors are shrinkage of stromal-cell nuclei; increasing fibrosis from the tunica albuginea, hyalinization of reticulum and vascular adventitia, and increasing numbers of germinal inclusion cysts. Conversely, in ovarian stromal hyperplasia, the cortex appears dense with stromal cells grouped into whorls and fascicles. In addition, the nuclei are bluntly oval rather than spindle shaped with the chromatin disposed at first loosely in a clear ground substance and subsequently gathered into large granules. Reticular fibrils become readily recognizable and collagen is scant. As this process regresses, there is a reduction in the size of the nucleus with increasing amounts of collagen and the appearance of cortical granulomas. They stress the point that stromal hyperplasia is a generalized process and that "even a small amount of available cortex in a given section may be sufficient to make the diagnosis." Using these criteria, they studied the ovaries from 331 patients with uterine carcinoma and 307 control ovaries obtained from autopsy specimens. These were within equal age ranges. Their results showed ovarian stromal hyperplasia in 84 per cent of the patients with carcinoma but in only 44 per cent of the controls. They found germinal inclusion cysts in 87 carcinoma patients and 54 controls, cortical granulomas in 26 carcinoma patients and 4 controls, thecomatosis in 12 carcinoma patients and 3 controls, and thecomas in 18 carcinoma patients and 2 controls. In their discussion, the authors raised the question of the possibility that the ovarian stromal hyperplasia is caused by the endometrial cancer, rather than the reverse.

Novak and Mohler[5] repeated the study of Woll and his associates and found similar relationships. In 63 patients with carcinoma, the ovaries of all of whom showed some degree of activity, they found 46 per cent of the ovaries to show minimal stromal changes and 54 per cent to show more marked hyperplasia. In the control group of 48 autopsy specimens, 78 per cent were atrophic ovaries and 21 per cent showed hyperactivity. They were unable to correlate conclusively the degree of hyperactivity with the histologic grade of the tumor, but found a suggestion that marked ovarian stromal changes were present predominantly in lesser grades of carcinoma.

Shippel,[7] in discussing the "hyperthecosis syndrome," postulates that ovarian stromal hyperplasia is an end result of this syndrome which begins earlier in life with different manifestations at different stages of life. He did not relate these changes to endometrial carcinoma at this time.

Sommers and Teloh[11] found an incidence of 83 per cent stromal hyperplasia in patients with carcinoma of the breast and only 37.6 per cent in control patients. Sommers and Lombard[10] correlated ovarian stromal hyperplasia

with cancers of the stomach, lungs, and esophagus, as well as the endometrium, but found no correlation in cervical and colon carcinomas. Emil Novak,[6] discussing this problem, stated that even though some of these correlations have been described, it has not yet been shown that ovarian stromal hyperplasia is an important source of estrogen. Smith[8] concurred in this in his discussion of nonmalignant lesions causing bleeding.

In a series of 13 theca-cell tumors studied by Sternberg and Gaskill,[12] the opposite ovary was available for study in 10. Of these patients, 8 were in the fourth decade, and all showed a "significant degree of ovarian stromal hyperplasia." None of these patients had endometrial carcinoma.

In the light of the foregoing information, two points came to mind which touched off the present investigation. First, it was the impression in this laboratory that the described changes had been seen quite frequently in ovaries from otherwise normal women and, second, the advisability of using autopsy material as controls was questioned because (1) some degree of degenerative change due to autolysis would be present in the control but not in the operative (carcinoma) specimens, and (2) it is possible that the structure of the ovary might be modified by the acute or chronic stress suffered by the individuals in the control group. Therefore, using what were considered more adequate controls, the following study was undertaken.

Method and Materials

The tissue used in this study was derived from two sources. The carcinoma cases were taken without selection from the files of the Departmental Laboratory and new sections were cut for special stains. None of the patients had been given preoperative radiation. A few of the control or normal specimens were also found in the files, the only selection being that they were from postmenopausal patients without endometrial carcinoma from whom the uterus and ovaries had been removed. The majority of the control specimens were obtained at operation from postmenopausal women undergoing vaginal hysterectomy and plastic operations for pelvic relaxations. The tissue was for the most part fixed in Bouin's solutions, although some of the earlier cases were formalin fixed. All were fixed immediately upon removal.

A total of 82 cases was studied, 42 controls and 40 carcinomas. These women were at least one year postmenopausal by history with the exception of 2 from both groups. The age range for each group is given in Table I and can be seen to be essentially the same.

TABLE I. AGE RANGE OF PATIENTS IN CARCINOMA AND CONTROL GROUPS

AGE RANGE	CARCINOMAS	CONTROLS
40-44	1	2
45-49	1	4
50-54	13	13
55-59	10	5
60-64	10	10
65-69	4	5
70-74	1	3

Three sections of ovary were studied from each case. The sections were from adjacent levels of the same block and were stained, respectively, with

hematoxylin and eosin, Milligan trichrome, and the Wilder reticulum stain with a hematoxylin and eosin counterstain. In this manner it was hoped to show any differences in collagen and reticulum more clearly than with the one routine stain.

The slides were then studied by the two observers independently. For the most part the ovarian tissue was studied and classified prior to examination of the uterus but not in all cases by both observers. A completely blind study would have been better, but a great effort was made to be absolutely impartial in all cases. The two sets of observations were then compared and all points of significant discrepancy restudied and clarified. The resulting combined opinions were then used in the final interpretation.

The criteria set up by Woll and his associates were used. Each set of slides was studied and tabulations were made of the number of germinal inclusion cysts and cortical granulomas, presence of thecosis, nuclear size and shape, relative amounts of collagen and reticulum, and sclerosis of ovarian blood vessels. Thecosis was determined by the presence of cells or groups of cells with increased cytoplasm and a definite cell membrane, the nuclei of which were round or oval. Over-all nuclear configuration was studied from the point of view of approximate relationship between the number of round-oval nuclei and spindle-shaped nuclei. Other structures looked for and tabulated were hilar cells and any other pathology present in the ovary. The uterine sections were studied for atrophy of myometrium, evidenced by a paucity of cytoplasm in muscle cells and thus a crowding of nuclei, and for the status of the endometrium.

In final interpretation of the results, all factors were not used. The estimate of the relative percentage of spindle to round-oval nuclei proved to be unreliable, as did an attempted estimate of the relative number of cells showing cytoplasm. The presence of cortical granulomas, thecosis, and the relative amount of collagen were the factors which were thought to be the most clear-cut and which could be objectively interpreted. In all cases the number of reticulum fibers was inversely proportionate to the amount of collagen, so its inclusion would be redundant. Unlike others, we found considerable variation in different areas in sections from some ovaries. In such instances the average of the findings in various areas was used.

Results and Comment

Table II summarizes the results. Diffuse thecosis was present in 11, or 26.2 per cent of the control cases (Fig. 1) and 10, or 25.0 per cent, of the carcinomas (Fig. 2). This disagrees with the previously cited findings of other workers. The fact that as many of our controls showed this finding as did those with carcinoma makes us doubt any significant relation between thecosis and carcinoma.

TABLE II. OVARIAN FINDINGS IN CARCINOMAS AND CONTROLS

	HILAR CELLS	CORTICAL GRANULOMAS	GERMINAL INCLUSION CYSTS	THECOSIS
Carcinomas	13	15	26	10
Controls	15	19	28	11

"Cortical granulomas" were found in 19, or 45.2 per cent, of the controls and 15, or 37.5 per cent, of the carcinoma series. These differences are not

significant. More interesting is the relative occurrence of "cortical granulomas" and germinal inclusion cysts in the same specimens. In both the carcinomas and controls, the great majority of cases with "cortical granulomas" also had germinal inclusion cysts, only 3 being without in the controls and 2 without in the carcinomas. The reverse was true in regard to thecosis. Of those with cortical granulomas only 6 in the control group and 3 in the cancer group had thecosis. There thus seems to be a greater relationship (or at least a more common association) of "cortical granulomas" to germinal inclusion cysts than to thecosis.

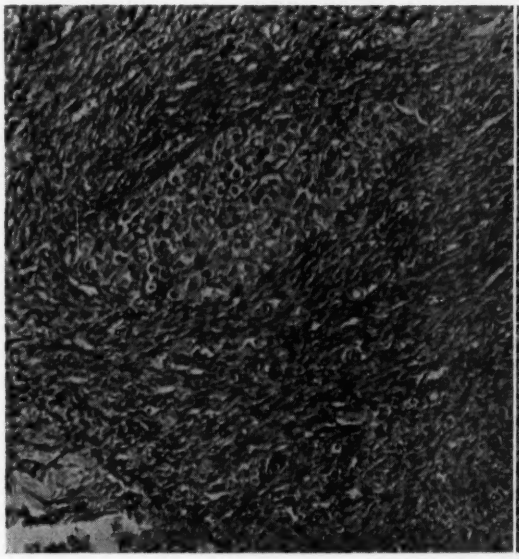

Fig. 1.

Fig. 2.

Fig. 1.—NUMS 21123. Area of thecosis in ovary from patient with atrophic endometrium. Note clump of large pale-staining cells. (×140.)

Fig. 2.—NUMS 22529. Areas of thecosis in ovary from patient with endometrial carcinoma. Note clumps of large pale-staining cells. (×140.)

The incidence of hilar cells was for practical purposes the same, being 13, or 32.5 per cent, in the carcinomas (Fig. 3) and 15, or 35.7 per cent, in the controls (Fig. 4). This is in agreement with the work of Greene and Peckham[1] who found these cells in patients both with and without endometrial carcinoma.

The most difficult factor to assess was the amount of collagen found in the ovarian stroma. This of course is a subjective estimation based on comparison with other sections of ovaries with similar stains, namely, Milligan trichrome. An effort was made to estimate the amount of collagen in each ovary and place it in one of five categories varying from slight to marked.

For the sake of completeness, these data are shown in Table III. In retrospect, it seems very doubtful whether, if the material were restudied, we could always clearly differentiate an ovary in the "slight to moderate" group from one in the "moderate" group; or could we distinguish one of the latter from one in the "moderate to marked" group. One could not, however, confuse an ovary having little or no collagen from one of the intermediate group.

Similarly, one could not confuse an ovary with a "marked" amount of collagen from one of the intermediate groups. The data on collagen were therefore reclassified into three more distinct groups (slight, intermediate, and marked) in Table IV. Three ovaries from both series were markedly fibrotic (Figs. 5 and 6). Three from the carcinoma group and 8 from the controls had very little collagen and were thus very "cellular" in appearance. The remaining in each category fell into the "intermediate" group. We do not believe that the difference between our two groups means anything more than a sampling error due to the small size of the groups.

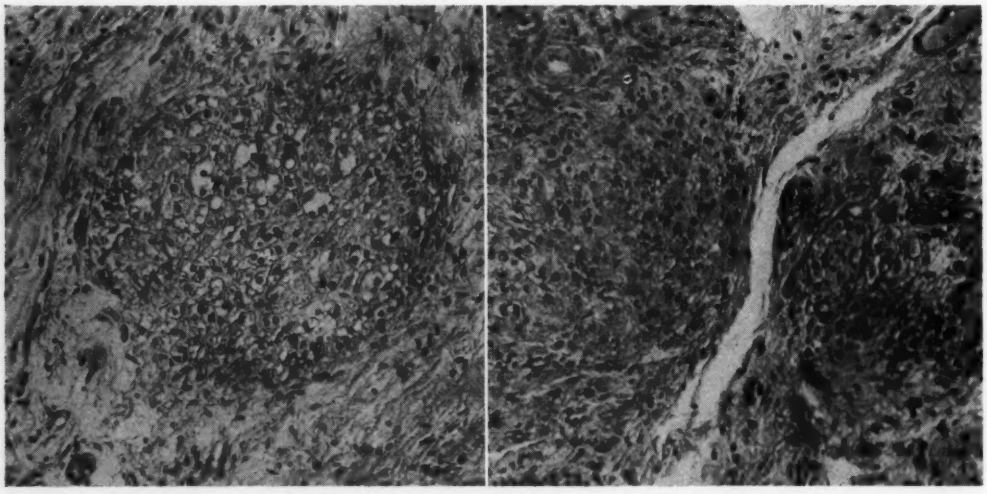

Fig. 3. Fig. 4.

Fig. 3.—NUMS 21663. Clump of hilar cells in ovary from patient with endometrial carcinoma.

Fig. 4.—NUMS 11151. Clumps of hilar cells in ovary from patient with atrophic endometrium.

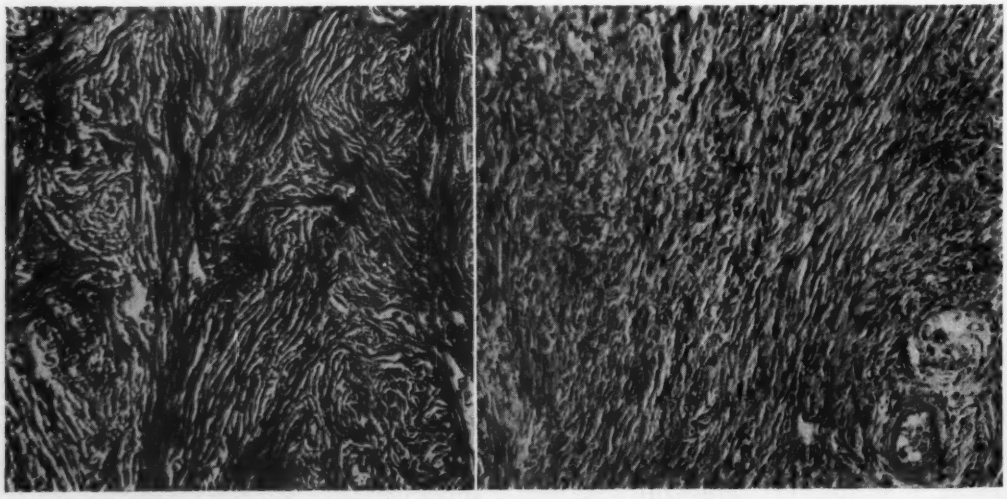

Fig. 5. Fig. 6.

Fig. 5.—NUMS 19886. Section of ovary from patient with endometrial carcinoma showing marked amount of collagen. (Milligan trichrome stain. ×150.)

Fig. 6.—NUMS 11187. Section of ovary from patient with atrophic endometrium showing marked amount of collagen. (Milligan trichrome stain. ×140.)

TABLE III. THE AMOUNT OF COLLAGEN IN CANCER AND CONTROL OVARIES

	COLLAGEN				
	SLIGHT	SLIGHT-MOD.	MOD.	MARKED-MOD.	MARKED
Carcinomas	3	5	21	8	3
Controls	8	9	16	6	3

TABLE IV. RECLASSIFICATION OF AMOUNTS OF COLLAGEN

	SLIGHT	INTERMEDIATE	MARKED
Carcinomas	3	34	3
Controls	8	31	3

If the stromal hyperplasia as such were more prevalent in cases with endometrial carcinoma, one would expect to find a higher per cent of ovaries with small amounts of collagen. This was obviously not the case. As previously stated, the amount of reticulum present in each was inversely proportionate to the amount of collagen, so these findings need not be elaborated upon except in so far as they served as a check on the estimation of collagen in each case.

Included in the control group were 31 cases showing atrophy of the endometrium, 12 with some cystic change in the glands. In 4 endometria there was evidence of previous hyperplasia now inactive. Three were hyperplastic and 4 were proliferative (Table V). Atrophy was manifest by a thin layer of endometrium with normal stroma and only a few glands with low columnar epithelium, the nuclei showing no evidence of activity. Those with cystic change were similar except for the presence of occasional dilated glands, again with no evidence of cellular or nuclear activity. Hyperplasia was judged to be inactive when no mitotic figures were present. The uterine sections were further studied for other pathology.

TABLE V. STATUS OF ENDOMETRIUM IN CONTROL CASES AND UNINVOLVED ENDOMETRIUM IN CARCINOMA CASES

STATUS OF ENDOMETRIUM	CARCINOMA	CONTROLS
Atrophic	19	31
(With cysts)	(3)	(12)
Hyperplasia	4	3
Inactive hyperplasia	0	4
Proliferative	2	4
No uninvolved endometrium	15	-
Total	40	42

In 25 of the 40 cases of endometrial carcinoma, there were sections of uninvolved endometrium available. These were studied for any changes that may have been present and the results given in Table V. The findings were similar to those in the control series. These endometrial findings and their relationships to those of the ovaries will be discussed at greater length in a subsequent communication.

Other pathologic conditions which were seen in the sections studied are listed in Table VI. The serous cystadenomas were microscopic lesions. The endometrial adenoma seen in one control case had no apparent cellular activity. Carcinoma of the rectum was diagnosed in one control patient two weeks after the vaginal hysterectomy and plastic operation which furnished the tissue studied here. The patient with preinvasive carcinoma of the cervix was a 51-year-old gravida iv, para iv, who also had uterine fibroids and atrophic endometrium.

TABLE VI. OTHER PATHOLOGIC CONDITIONS

	CONTROLS	CARCINOMAS
Ovary.—		
Small serous cystadenoma	3	0
Oophoritis	0	1
Uterus.—		
Fibroid	2	0
Adenomyosis	0	1
Endometrial adenoma	1	0
Endometrial polyp	1	0
Preinvasive carcinoma of cervix	1*	0
Other.—		
Carcinoma of rectum (Diagnosed post-operatively)	1†	0

*Ovary in patient with carcinoma of cervix, aged 51 years, showed no thecosis or hilar cells and 3 cortical granulomas. There was a slight to moderate amount of collagen in the cortex.

†Ovary in patient with carcinoma of rectum, aged 65 years, showed no thecosis or hilar cells and 3 cortical granulomas. There was no marked amount of collagen in the cortex.

Summary and Conclusions

A summary of the literature implicating an ovarian change called stromal hyperplasia in the evolution and/or etiology of endometrial carcinoma has been presented. Proponents of this concept found what appears to be a significant increase in the occurrence of this change in patients with carcinoma of the endometrium as opposed to those without.

Microscopic changes in ovarian histology which lead to this diagnosis include increased cellularity with increased cytoplasm in stromal cells accompanied by enlargement and blunting of nuclei, a feature unlike the usual spindle-shaped variety. These changes, when marked, would be similar to or the same as thecosis, either diffuse or patchy. Other important findings are cortical granulomas and a relative or absolute decrease in the amount of collagen expected in atrophic ovaries with the reciprocal increase in reticulum. It has been stated that these changes are more evident and more common in the ovaries of persons with endometrial carcinoma than in those without endometrial cancer. That work is based on ovaries from patients with carcinoma obtained at operation and those of the controls at autopsy.

The present study includes 42 control cases and 40 carcinoma cases. The preparations from both groups were from fresh surgical specimens. This study failed to confirm the previously reported findings in that there was no significant difference between the ovaries of those with and those without endometrial cancer.

It appears from the findings in the reported small group that there are no specific changes yet reported in ovaries from women with endometrial carcinoma which cannot also be found in equal degree in those without endometrial carcinoma.

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Discussion

DR. JOHN I. BREWER.—The significance of cortical hyperplasia is questioned; it is not proved that these tissues produce estrogen. It is not proved, if they do produce this hormone, that the quantity is excessive or that it is capable of inducing carcinoma of the endometrium.

If estrogen is present in sufficient amount to act as an important agent in the activation of endometrial carcinoma, then it would be reasonable to presume that it would stimulate to some extent those portions of the endometrium not involved in the malignant change. The present authors did not find this to be true. They found those portions to be no different than the endometria in patients without carcinoma. Fahlund and Broders and others have reported that the type of endometrium is the same in uteri with carcinoma and those without carcinoma. Jones and Brewer have observed evidence of normal ovarian function in a sufficient percentage of women in active menstrual life who have endometrial carcinoma to indicate that there is frequently no support for the theory that excessive estrogen or unopposed action of this hormone is important in the etiology of this type of cancer. We also found that the endometrium not involved in the malignant change frequently responded in a normal fashion to both estrogen and progesterone stimulation: in other words, the uninvolved endometrium and the ovarian function continued in a normal manner despite the development and progression of endometrial carcinoma. Cianfrani presented rather concrete evidence that ovarian estrogen is not essential for the development of endometrial carcinoma. He reported the eventual outcome of 130 patients who had bilateral oophorectomy without hysterectomy. Eight developed endometrial carcinoma 5 to 30 years after the bilateral oophorectomy. The average number of years between the surgical procedure and the diagnosis of the malignancy was 10.6. This leaves no doubt that this type of cancer does arise in the absence of ovarian estrogen stimulation.

On the other hand, there is evidence presented by excellent workers which suggests that estrogen may play a part in inducing endometrial carcinoma. In view of this conflict of evidence it is apparent the question cannot be solved at this time and that we should all retain an open mind despite our unavoidable leaning toward one point of view as a result of personal observations.

The authors quoted the work of Sommers and Teloh in which stromal hyperplasia was found in 83 per cent of 100 patients with breast carcinoma who came to necropsy. Sommers and Teloh also said that this stromal hyperplasia is morphologic evidence of antecedent excessive estrogen secretion and together with other evidence emphasize the importance of endocrine factors in the etiology of breast carcinoma. In the same year Sommers, with McManus, reported that the survival time in patients with breast cancer and ovarian cortical stromal hyperplasia was 41 months and in those patients with breast cancer with no ovarian stromal hyperplasia it was only 23 months. How can this be explained? Reasoning along the line that McManus and Sommers and others have done, the mere coexistence of stromal hyperplasia and endometrial or breast carcinoma signifies a cause-and-effect relationship. If this is suitable, then one might and probably should continue that type of reasoning to interpret the findings of McManus and Sommers. It would thus be: the stromal hyperplasia produces excessive estrogen which has an effect

in the production of breast cancer and then, since patients with stromal hyperplasia and excessive estrogen live longer than those with no ovarian stromal hyperplasia and no estrogen, the excessive estrogen and stromal hyperplasia must in some way exert an effect which slows the growth of the cancer it has produced and also in some way prolongs the life of the patient. McManus and Sommers state the cause-and-effect relationship is significant as far as the formation of the cancer is concerned but do not continue this same cause-and-effect line of reasoning to the obviously similar relationship that the stromal hyperplasia and excessive estrogen are significant as far as the slower growth of the cancer and prolongation of life are concerned.

From all this one thing is certain, stromal hyperplasia occurs with and without carcinoma of various organs but its etiological significance remains unproved.

In the study of stromal hyperplasia Roddick and Greene have implied the possibility of a difference between the ovarian specimen obtained at autopsy and at operation. In their conclusions no mention is made of such differences. May I ask for their findings and for clarification on this point?

DR. GREENE (Closing).—Our main point is that in our small series there was no difference in the ovaries of patients with carcinoma and without carcinoma. We did not explain the difference between our results and those of our predecessors in this particular field. It is our intention to do a study of a third group, namely, the ovaries of patients without carcinoma who died of other causes and were autopsied. Be this as it may, our work and that of everybody else contains a very large fallacy. These data of ours and others show what was going on in the ovaries at the time the woman was operated upon. We do not know that the findings would have been the same some five or ten years ago when carcinoma started in the endometrium.

SERUM ALBUMIN FRACTIONS OF DIFFERENT SOLUBILITY AND THEIR RELATION TO CANCER*

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THE difficulties in the clinical diagnosis of malignancies led to many attempts to develop a serological method which could be used as a diagnostic aid.[3, 8, 9, 10, 19] Kahn had observed that sera from patients with malignant tumors had a lower binding capacity for certain tissue extracts (e.g., pancreas) and for certain chemical substances, like sodium oleate. Free oleate in very small amounts causes hemolysis and precipitation of globulin in serum. These properties were used to measure in a number of sera their binding capacity for added sodium oleate.[11, 12] It was observed that this binding capacity was fairly constant in normal sera, while it was considerably lower in about 80 per cent of the sera from patients with malignant tumors (hereafter called "cancer sera") and in about 20 per cent of sera from patients with diseases other than malignancies (called "noncancer sera"). A correlation of binding capacity for oleate and albumin concentration was found although it was not strictly proportional.[12, 13, 14] It could be demonstrated during studies on precipitation of serum proteins that in concentrations of ammonium sulfate between 35 and 40 Gm. per cent a greater part of the albumin was precipitated in cancer sera than in noncancer sera.[14-17] It was thought that cancer sera were deficient in the more soluble albumin fraction, called Albumin A.[14, 15] Much time was spent in improving the methods for its estimation and its purification.[1, 18, 21] The original concept that Albumin A is chemically different from the other serum albumin fractions[5] could not be confirmed by extensive studies on purified albumin preparations from normal, cancer, and noncancer sera.[21]

Thirty or more methods were used on several thousand sera for estimation of the more soluble albumin fraction. Here only one method and the results obtained by its use will be reported.

Method

General Principle.—Serum was pipetted onto a strip of humid filter paper. By immersion of the strip with the serum into a nearly saturated ammonium sulfate solution all the proteins were precipitated on the paper. By subsequent immersion of the paper with the precipitated serum proteins into an ammonium sulfate solution of lower concentration (38.5 Gm. per cent) for a definite time

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a part of the albumin was extracted, which was designated as the more soluble albumin. The extract was heated for 3 minutes in a boiling water bath, and after cooling the formed turbidity was read in an Evelyn photoelectric colorimeter with a 420 filter. The instrument was set at 100 using the same ammonium sulfate solution as blank. The number G (per cent of light transmission) can be transformed into gram per cent albumin according to Beer's law. Theoretically the concentrations of different albumin solutions are proportional to their (2–log G) values, but we found that within certain limits of G their (100–G) values can be used to calculate the ratios of their concentrations.

Preparation of the 38.5 Gm. Per Cent Ammonium Sulfate Solution.—Weigh 770 Gm. of pure ammonium sulfate and transfer with about 1,500 ml. water into a 2 L. volumetric flask. Add 9 ml. of 85 per cent (16.3 M) H_3PO_4, mix. Add about 18 ml. of concentrated NH_4OH (about 18 M) and fill, after the salt is dissolved, to the 2 L. mark with water. Compare the pH with a standard phosphate buffer of pH 7.2 using phenol red as an indicator. If necessary, adjustments of the pH can be made by the addition of small amounts of concentrated NH_4OH or concentrated H_2SO_4. The 31 and 48 Gm. per cent solutions were prepared correspondingly by weighing 620 resp. 960 Gm. of ammonium sulfate and using 16 ml. NH_4OH to achieve a pH of 6.8.

Preparation of the Filter Paper Strips.—No. 595 filter paper (Schleicher and Schüll) is cut into strips 9 by 87 mm. and 8 by 52 mm. A hole of 6 mm. diameter is punched with its center about 6 mm. from one end of the strip. A group of such strips is suspended from the hook in the stopper of a bottle containing water, to saturate them with water vapor. They remain there for at least 12 hours, and then are singly suspended in water vapor for at least 5 minutes before the start of the experiment.

Procedure for the Paper Extraction Method.—Measure 0.05 ml. serum onto a humid filter strip 9 by 87 mm., expose for 5 minutes to water vapor, immerse for at least 7 minutes into a test tube containing 15 ml. of a 48 Gm. per cent ammonium sulfate solution of pH 6.8. Transfer after drainage into a 16 by 150 mm. test tube containing 15 ml. of a 38.5 Gm. per cent ammonium sulfate solution of pH 7.2. Let stand in the tightly stoppered tube at room temperature for 44 to 48 hours. Remove paper, heat the extract, and read G as described.

Estimation of Total Albumin.—Measure 0.03 ml. serum onto a humid filter strip 9 by 52 mm., and after 5 minutes' exposure to water vapor immerse directly into an 18 by 150 mm. test tube containing 20 ml. of a 31 Gm. per cent ammonium sulfate solution of pH 6.8. Extract for about 24 hours, remove paper, heat the extract, and read G.

The standard deviation was 7 per cent for the estimations of the more soluble albumin fraction, and 2 per cent for total albumin. For this reason quadruplicates were done for the estimations of the more soluble albumin, and duplicates for total albumin. On the average, a value of 1.13 Gm. was found for the more soluble albumin in 100 ml. of normal serum, which is about 25 per cent of its average concentration of total albumin (4.5 Gm.). It was observed that estimations of the more soluble albumin fraction repeated on the same serum on different days showed variations up to 15 per cent, while the ratio of the values of different sera remained constant within the standard deviation. This demonstrates that the variations of the results observed on different days on the same sera were not caused by changes in the sera, but by changes in the experimental conditions (concentration or pH of the solutions, temperature, extraction time, etc.). For this reason we included in each experiment one or several known normal sera and instead of giving the results in

Grams per cent protein we preferred to give them in S and T. S is defined as $\frac{(100 - G_E)}{(100 - G_N)} \times 100$. The scale divisions read on the colorimeter for the normal or the average of several normal sera are given by $(100 - G_N)$, while $(100 - G_E)$ refers to the scale divisions read for the examined serum. Since we observed fewer variations for total albumin estimations on different days, we used for calculation of T the same denominator, i.e., $(100 - G)$ corresponding to a concentration of 4.5 Gm. albumin in 100 ml. serum.

Comparison of Plasma and Serum.—Oxalated plasma and serum obtained from blood of the same patient, drawn at the same time, and examined in the same experiment, showed only variations within the standard deviation. We have used plasma and serum interchangeably when only plasma was available.

Storage of Serum.—Repeated examination of sera kept in the refrigerator revealed little change during the first two weeks of storage, as long as no spontaneous turbidity or precipitation occurred in the samples. Freezing caused considerable change in the analytical values of some sera, and should be avoided.

Effect of Food Intake.—Comparative estimation of the more soluble albumin fraction in the serum from blood of the same person drawn in the postabsorptive stage (at least 12 hours after the last meal) and 1 to 2 hours after a meal rich in fat, showed increases of 20 to 100 per cent in the second sample. For diagnostic purposes serum from blood drawn in the postabsorptive stage must be used, to avoid serious errors in the serological evaluation.

Clinical Studies.—Between February, 1950, and December, 1951, sera were obtained from 684 women from the Chicago Lying-in Hospital. Among them were 14 pregnant patients and 207 patients with gynecological carcinoma, 108 of whom were examined repeatedly at intervals of several months clinically and serologically.

The purpose of this study was to determine the suitability of the method for ascertaining whether or not the surgical or irradiation treatment or both were sufficient. If by such a test it could be shown that after initial treatment malignant growth still persists, more intensive treatment could be given immediately, before clinical signs of recurrence become detectable, and thereby the survival rate increased.

Clinical Evaluation.—All diagnoses of malignancies were confirmed by histological examination. The evaluation of the therapeutic success was based on clinical findings or repeated biopsy. The treated cases were classified as (a) nonrecurrence, (b) recurrence, progression, or death from carcinoma, and (c) doubtful, when classification in a or b was not possible.

Serological Evaluation.—In the first part of this study the S values (per cent of normal) were classified for correlation with clinical evaluation as high, intermediate, and low by arbitrary selection of an intermediate zone of 64 to 81 for S. A similar evaluation had been used in previous studies with different methods.[4, 6, 15, 16]

Results of This Evaluation.—In Table I is given the correlation of the 3 classes of serological evaluation to clinical diagnosis. This correlation was incorrect in 1 per cent of the noncancer sera (false positives), and in 29 per cent of the untreated carcinomas (false negatives). About a third of the sera in each group were classified as intermediate. The correlation between clinical and serological evaluation of the success of treatment of gynecological carcinoma was even less satisfactory, as shown more in detail in Table II.

TABLE I. CLASSIFICATION OF S VALUES* IN NONMALIGNANCIES AND IN TREATED AND UNTREATED GYNECOLOGICAL CARCINOMA. SEROLOGICAL EVALUATION BY SEPARATING THE S VALUES INTO HIGH (NEGATIVE), INTERMEDIATE, AND LOW (POSITIVE) BY CHOOSING ARBITRARILY AN INTERMEDIATE ZONE (64 to 81)

TOTAL CASES	NEGATIVE	% OF TOTAL	INTERMEDIATE	% OF TOTAL	POSITIVE	% OF TOTAL
431 nonmalignancies	333		94	22	4	1
56 carcinomas before treatment	16	29	18	32	22	
48 carcinomas from the 56 listed above after treatment						
25 nonrecurrence	9		9	36	7	28
8 doubtful	3		1		4	
15 recurrence	1	7	5	33	9	
97 carcinomas examined only once after treatment						
81 nonrecurrence	65		16	20	0	0
3 doubtful	0		1		2	
13 recurrence	1	8	0	0	12	
110 carcinomas examined more than 2 years after initial treatment						
102 nonrecurrence	75		21	21	6	6
8 recurrence	3	37	2	25	3	

*S means concentration of the more soluble serum albumin fraction expressed in per cent of average normal.

TABLE II. CHANGES* IN S VALUES† AMONG 63 TREATED PATIENTS WITH GYNECOLOGICAL CARCINOMAS WHO WERE REPEATEDLY EXAMINED CLINICALLY AND SEROLOGICALLY

	S VALUES†		
	INCREASE OR REMAIN HIGH	REMAIN INTERMEDIATE	DECREASE OR REMAIN LOW
26 patients examined before and after treatment			
16 nonrecurrence	10	6	0
4 doubtful	4	0	0
6 recurrence	0	2	4
36 patients examined several times after initial treatment only			
26 nonrecurrence	17	5	4
1 doubtful	1	0	0
9 recurrence	0	1	8

*As change was considered increase or decrease of the S value of more than 10 in consecutive examinations of sera from the same patient in intervals of one or more months after treatment.

†S means concentration of the more soluble serum albumin fraction expressed in per cent of average normal.

As data accumulated, we recognized the interdependence of S and T. While in the beginning T had been determined only in sera with low S, it was estimated in all sera during the second part of this study. It became evident soon that only a few sera with low T were obtained from the ambulatory noncancer patients from Chicago Lying-in Hospital. To be able to compare noncancer and cancer sera with the same T, we included in Table III the results obtained from 97 sera from patients who were in other hospitals of the University of Chicago. Among them were 17 with active malignancies. Twelve noncancer sera with very low T were not included in Table III, since there were no cancer sera with similar T in this series. It may be mentioned that not only the S values, but also the S/T ratios were much lower in these sera

than in the higher T ranges (see also Fig. 1). When the noncancer and cancer sera were separated into 7 different T ranges (Table III) it was found that the S values within the same T range varied considerably. The maximum and minimum S values in each group of sera overlap in the different T ranges, and also the maximum S values of the cancer group overlap with the minimum S values of the noncancer group within the same T range. A more regular trend could be demonstrated by calculating the average S for each T range. In both groups the S values decrease with decreasing T, and in each T range the average S is considerably lower in the cancer than in the noncancer group. But it may be noticed that the average S values of the noncancer sera in the low T ranges are lower than the average S values of the cancer sera in the high T ranges. This leads to the conclusion that a satisfactory serological evaluation requires comparison of noncancer and cancer sera of the same total albumin concentrations.

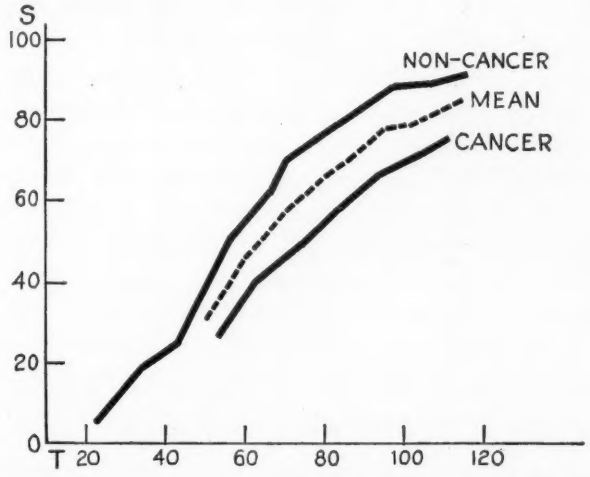

Fig. 1.—Shows S value for each value of T. S values above the curve of the mean were called negative for cancer and below the mean were called positive for cancer.

To make this possible the average S for the average T in each T range was plotted for noncancer and cancer sera separately, so that 2 curves could be drawn (Fig. 1). A third curve, called the curve of means, was drawn in equal distance between these 2 curves. The analytical result for each serum was classified as high or low corresponding to the position of the individual S for the individual T either above or below the curve of means. The correlation of this evaluation with clinical diagnosis of carcinoma is shown in Table III. Of the total of 464 noncancer sera, 72 or 16 per cent had low S values, and of the total of 82 cancer sera 6 or 7 per cent had high S values. One may notice that the distribution in the different T ranges is unequal between the 2 groups of sera, and also that the percentage of false positives and false negatives varies considerably in the different T ranges. When we equalized for these variations by calculating the grand average we obtained 78 per cent correct evaluations for the noncancer, and 89 per cent correct evaluations for the cancer sera.

Separately listed in Table IV are the results of the serological evaluation of the available data for untreated and treated gynecological carcinoma with the curve of means. Compared with Table I it shows a definite improvement in the correlation between clinical and serological evaluation, especially in the

cases with recurrence, but the high number of false evaluations in the cases with nonrecurrence interferes seriously with the clinical usefulness of this method.

In addition to the sera reported in Tables I to IV, 14 sera from patients with pregnancies of different duration of gestation and 2 sera from the umbilical cord blood, obtained during delivery, were analyzed. S and T decrease with

TABLE III. SPREAD OF S VALUES* AND THEIR AVERAGES IN DIFFERENT RANGES OF T†, AND CORRELATION OF THE INDIVIDUAL S VALUES WITH THE CLINICAL DIAGNOSIS OF MALIGNANCY BY USE OF THE CURVE OF MEANS‡

T† RANGE	NUMBER OF CASES	AVERAGE S	S RANGE	EVALUATION‡		PER CENT CORRECT§
				POSITIVE	NEGATIVE	
464 Sera From Nonmalignancies.—						
110-119	67	91	115-74	6	61	91
100-109	187	89	110-69	26	161	86
90-99	146	88	105-67	24	122	84
80-89	30	79	90-48	4	26	87
70-79	13	72	102-44	5	8	62
60-69	15	61	94-32	5	10	67
50-59	6	50	88-35	2	4	67
Average		76				78
82 Sera From Active Malignancies.—						
110-119	3	75	90-65	2	1	67
100-109	7	71	73-61	6	1	86
90-99	27	66	76-43	26	1	96
80-89	19	58	72-52	18	1	95
70-79	7	49	52-34	6	1	86
60-69	16	40	53-35	15	1	94
50-59	3	26	30-5	3	0	100
Average		56				89

*S means concentration of the more soluble serum albumin fraction expressed in per cent of normal.

†T means concentration of the total serum albumin expressed in per cent of average normal (4.5 Gm. per 100 ml. serum).

‡Based on the position of S value for the particular T to the curve of the means (Fig. 1).

§Correct means high S values (negative) in nonmalignancies, low S values (positive) in active malignancies.

TABLE IV. S VALUES* FROM SERA OF PATIENTS WITH GYNECOLOGICAL CARCINOMA EVALUATED WITH THE "CURVE OF MEANS†" AND THE CORRELATION OF THE CLINICAL AND SEROLOGICAL EVALUATION TO THE SUCCESS OF TREATMENT

T‡ RANGE	UNTREATED			TREATED					
				RECURRENCE			NONRECURRENCE		
	TOTAL CASES	NEGATIVE	POSITIVE	TOTAL CASES	NEGATIVE	POSITIVE	TOTAL CASES	NEGATIVE	POSITIVE
110-119	-	-	-	2	1	1	7	6	1
100-109	2	1	1	5	0	5	15	8	7
90-99	5	0	5	21	0	21	19	13	6
80-89	5	0	5	13	0	13	2	2	0
70-79	-	-	-	5	0	5	-	-	-
60-69	5	0	5	8	0	8	-	-	-
50-59	1	0	1	-	-	-	-	-	-
Total	18	1	17	54	1	53	43	29	14
False serological evaluation in per cent of total		6			2				33

*S means concentration of the more soluble serum albumin fraction expressed in per cent of average normal.

†Based on the position of S value for the particular T to the curve of means (Fig. 1).

‡T means concentration of the total serum albumin expressed in per cent of average normal.

the duration of gestation, and S reaches the lowest value at term. During the last trimester the S values were below the curve of means. The S and T values in the sera from the blood of the umbilical cord did not differ significantly from the average values observed in normal adults.

The methodological and clinical studies were continued during the following years. It was tried to explain the clinical results by experiments in vitro. It was found that the S values of normal sera can be altered by addition of certain lipids.[7] It could be demonstrated that a certain lipid fraction extracted from cancer sera caused more lowering of S values of normal sera than a lipid fraction prepared with the same method from noncancer sera. A similar difference was observed between the effect of a certain lipid fraction from cancer and normal tissues. It was found that addition of globulin to serum lowers its S value.

A new method was developed in which the more soluble albumin fraction, total albumin, and globulin were separated from mixtures of serum and ammonium sulfate solutions of different concentration by use of a high speed angle centrifuge. Analyses with this method showed that the value obtained for the more soluble albumin fraction does not depend on the concentration of the total albumin, but on the ratio (albumin + globulin) to albumin. The shape of the curves in Fig. 1 can be explained by the fact that on the average this ratio is higher in sera with lower total albumin. The variations of S values of different sera within the same range of T are caused mostly by variations of their globulin concentrations. The effect of changes in the globulin concentration may overshadow the altering effect of nonprotein substances on the S values. Since globulin estimations were not carried out in the sera used for this study a correction for its variations cannot be applied. It is known that in many of the nonmalignant conditions, like infections and liver diseases, in which false positive evaluations were obtained, the ratio total protein/albumin is usually increased, and a similar change was reported after irradiation.[2, 20] This may explain many of the false positive evaluations obtained in cases of carcinoma after successful irradiation treatment. Most of the false negative evaluations in patients with untreated carcinoma were observed in cases with localized nonnecrotic tumors. In such cases the total protein/total albumin ratio is frequently decreased.[14] These considerations and the results of our more recent clinical studies justify our assumption that the correlation between serological and clinical evaluation would be much better after correction for the variations in the globulin concentration or in other words when cancer and noncancer sera with the same albumin and globulin concentration would be compared. This consideration may apply also to many of the other "cancer tests." The details of the new method and the results obtained will be reported elsewhere.

Summary

1. A method is described in which the more soluble albumin fraction is extracted with a 38.5 Gm. per cent ammonium sulfate solution from the serum proteins precipitated on a strip of filter paper. The total albumin was estimated

by extraction of serum absorbed on a filter strip with a 31 Gm. per cent ammonium sulfate solution. The protein concentration in the extracts was measured turbidimetrically. On the average 100 ml. of normal serum contained 1.13 Gm. of the more soluble albumin fraction which represents about 25 per cent of the total albumin.

2. The values for the more soluble albumin fraction, expressed as S = per cent of average values in normal sera, and the values for total albumin, expressed as T = per cent of average normal total albumin, were measured in 464 nonmalignancies and 82 malignancies. In addition S alone (without T) was determined in 320 nonmalignancies and 157 malignancies.

3. For correlation with cancer diagnosis, S values were classified in two ways: first as high and low with respect to an intermediate zone which bears no relation to T, later as high and low with respect to a curve (Fig. 1) which represents the mean of the averages of S values in nonmalignancies and in malignancies for each T. The advantages of the later classification are pointed out. On the average the S values were 23 per cent lower in the sera from malignancies. Evaluation of the individual sera with the curve of means (Fig. 1) was correct in 89 per cent of the malignancies and in 77 per cent of the nonmalignancies. The correlation with the clinical evaluation of the success of treatment of gynecological carcinomas was correct in 98 per cent of the recurrences, and in 67 per cent of the nonrecurrences.

4. During pregnancy S and T values decrease with the duration of gestation, in the last trimester they become indistinguishable from those of malignancies.

5. Results from more recent studies indicate that the serological evaluation can be improved by a correction for the variations in the total protein/total albumin ratio.

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VISIONS AND REVISIONS*

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"For time is like a fashionable host,
That slightly shakes his parting guest by the hand,
And with his arms outstretch'd, as he would fly,
Grasps in the comer."

Shakespeare[1]

ALL progress is a function of time. In an earlier era the forward movement was slow but now we advance with bewildering speed. The stream of time seems to have changed from a meandering brook to an intellectual Missouri swollen by spring floods. Or is that merely our generation's slanted viewpoint? Lionel Trilling[2] states it well: "It has always been true that a chief reason for the alienation of one generation from another lies in their different understanding of what constitutes the past. In every age it must have been difficult for a man, and painful, to realize that some event which he still regarded as immediate and present in his own experience was, to a younger friend or colleague, merely a fact he learned from a book."

In addition to knowing the meaning of an epoch, we have also learned that no research is free from relation to other disciplines, whether the investigation has a limited objective such as determination of the heartbeat of a whale, or aims to solve a manifold mystery such as the cause of labor. No fact is unimportant, even though its value may lie merely in a passing enhancement of another, perhaps more esoteric, theory. Moreover, it is commonplace to observe that advances are made by the steppingstone technique, each step ahead depending upon the presence of a preceding one. Freud, for instance, was fond of pointing out that a dwarf perched on the head of a giant would be able to see farther toward the horizon than the giant.

The specialty of obstetrics and gynecology is more than a discipline for the marshaling of diagnostic methods and the treatment of patients. In common with other branches of clinical medicine, it leans heavily upon the basic sciences which are its nursery of ideas. In horticulture, all trees, shrubs, and vines propagated in a nursery do not survive transplanting despite careful fostering; nor do all become good stock for grafting. Thus, not all ideas, even though maintained in the selfsame soil, take hold; nor is it necessary that all of them be viable. One of the principal tasks of any generation of physicians is to recognize and to preserve the most valuable of the current crop. This cannot be done without an appreciation of what has gone before. We stand, as it were, on the head of a giant, attaining there our own stature.

The Lesson of Medical History

We must ever have a historical perspective. Without it, we cannot appraise a new theory or suggestion; nor can we decide whether or not to yield

*Address of the President, Obstetrical Society of Philadelphia, May 3, 1956.

a cherished viewpoint to it. More important, and more pertinent to this thesis, is that knowledge of our medical past makes us acutely aware that the last vision has never been seen and the last word has never been said on any subject. Such awareness should teach us to avoid dogmatic attitudes. Because of the past, we know that the pattern of progressive learning is never smooth but rather that it is delayed, troubled, reversed, and arrested in its forward motion by obstructions, blind alleys, clash of theories, and the pitfalls of misdirected effort. The struggle is continuous. On the one hand, there is the need to support that in which we firmly believe, yielding it to another viewpoint only when we are convinced of the second's value. On the other hand, we are beleaguered with new things daily and, without care, may welcome one improvidently. Pope pointed out that "some praise at morning what they blame at night, but always think the last opinion right." Blind advocacy of a habitually held opinion is as bad as the too quick acceptance of all that is new.

There is danger in both the acceptance and the giving up. The former, the acceptance, is made difficult because we are plagued by suggestions which are not sensible, unimportant distractions to which we should barely lend an ear as we brush them aside. The latter, the giving up, must be particularly judicious, preserving whatever is useful, for one must be careful to save the baby when he drains out the bath water. For these reasons, viewpoints need constant reviewing.

Even a haphazard backward glance will illustrate the continuing importance of Hippocrates' admonition that the physician "should make no pretense to infallibility." The annals of obstetrics and gynecology offer endless examples of our fallibility and, at the same time, show how our professional progenitors treated new ideas. One may, selecting at random, classify them as having been crackpotlike, stubborn advocates, and rediscoverers. Each of the following reminders of the past cautions us to be somewhat less than positive in our perishable pronouncements. We cannot, as Shakespeare emphasized, say, "I am Sir Oracle, and when I ope my lips let no dog bark."[3]

The Crackpot

The human brain, "house of a thousand fancies," is capable of devising orderly, practical systems as well as follies which have no connection with reality. Such incomprehensible suggestions may be found by hundreds in any historical analysis. Most of them, remaining the favorite child of their inventor, never grew to medical manhood, fortunately. As illustration, one may cite an ingenious douching apparatus and a projected method of examination.

Self-douching.—John Weiss, a maker of surgical instruments in London 100 years ago, devised a strange douching apparatus.[4] It consisted of a sitz bath raised upon 4 table legs, the seating surface being a mattresslike rubber bag. The latter was filled with water through an inlet at one end and connected by an outlet at the other end to a vaginal nozzle. The patient, placing the nozzle in her vagina, sat on the mattress and created a bellowslike effect. Her weight forced water from the rubber-bag reservoir through the douching system. Mr. Weiss described his "self-acting" apparatus as being "easy of application." Although publicized in 1867, it never gained acceptance and by the turn of the century was regarded with amusement.

The Water-Soaked Patient.—Paul Profanter[5] described a novel technique of gynecologic examination in 1906. He recommended that the patient be examined bimanually while she lay, half-reclining, in a tub of warm water. He ascribed two major advantages to this underwater method—the warm water would relax the tense abdomen of the patient and would in addition distend the vagina, making examination easier. Profanter acknowledged that the patient's undue exposure as she lay nude in the tub and the temporary discomfort of the knees and back of the gynecologist could be possible deterrents. However, he regarded them as minor objections in view of the alleged benefits. Happily, Profanter's suggestion was likewise not put into practice.

Stubborn Advocates

The whetstone of the intellect is the right to question, for it is this which sharpens the tools of our art. Any new proposition should be faced by some degree of healthy skepticism, for it is not wholesome to pretend to believe everything. A critical posture, encouraged during his school days, comes naturally to the physician. On the other hand, a sit-down strike to preserve the status quo is a hindrance to progress. There is a difference between the temporary acceptance of a working hypothesis, what Coleridge termed "the willing suspension of disbelief," and blind spots. The latter may endanger intellectual freedom and hamper growth. They are, nevertheless, universally encountered; historical examples from the pages of obstetrics and gynecology such as the two which follow, come easily to mind.

Vaginal Examination.—It seems strange now but 100 years ago it was not commonplace for women to submit to any type of vaginal examination. At that time, the use of the vaginal speculum was the center of a raging controversy, for many physicians found it objectionable, regarding it as an "instrument of unbridled indecency." Those who insisted upon its use had to defend their own morals as well as the diagnostic value of the speculum. The acrimonious debate persisted for half a century, eventually involving any type of vaginal investigation. Such an examination, termed "unprincipled" and described as being "repugnant to the feelings of women," was condemned by many prominent gynecologists. Among them was Charles D. Meigs,[6] Professor of Midwifery and Diseases of Women and Children at Jefferson Medical College, whose textbook (1848) took the form of letters addressed to his students. The introductory letter, consisting of a romantic tribute to the "genteel female" to whom Meigs attributed all the virtues of sweetness, purity, and light, serves to explain some of his attitudes. In reference to vaginal examination, he wrote, "He is but the pander of vice . . . and is himself an unchaste man who ruthlessly insists upon a vaginal taxis in all the cases of women's diseases . . . I am bound also to say that it will be your painful, even your distressing duty, to condescend to the task of making such explorations sometimes. . . . I confess I am proud to say that in this country generally, certainly in many parts of it, there are women who prefer to suffer the extremity of danger and pain rather than waive those scruples of delicacy which prevent their maladies from being explored. I am rejoiced at it; because, however inconvenient, and however baffling in the particular instances of suffering, it is an evidence of a high

and worthy grade of moral feeling." Such fulsome language of condemnation was typical of Meigs who was known for his trenchant, ex cathedra, dramatic style of lecturing and who, in his time, vigorously opposed not only vaginal examination but also the operation of ovariotomy, laparotomy for ectopic pregnancy, anesthesia in obstetrics, and the infectious origin of puerperal fever.

Gonorrheal Salpingitis.—Members of this generation of physicians, having found a means of reducing the ravages of gonorrheal salpingitis, may find it difficult to believe that the existence of this disease was seriously questioned less than 100 years ago. When Emil Noeggerath first offered his observations upon gonorrhea in women, suggesting that the disease might be manifested as acute or chronic inflammation of the Fallopian tubes, he had a most difficult time convincing physicians. It is to his credit that he deliberately chose to read a paper on this subject, entitled "Latent Gonorrhea, Especially With Regard to Its Influence on Fertility in Women," at the initial meeting of the American Gynecological Society in 1876.[7] A lively discussion followed his presentation, during which seven of the most prominent gynecologists opposed his views. I have no doubt that had not Noeggerath been one of the founding fellows of the American Gynecological Society he would not have been handled so delicately in the debate. It must have nonetheless been sufficiently disturbing to Noeggerath, for his closing words were significantly expressive: "After the gentlemen have given five years or more of careful study to this question, I shall expect to hear more approval than I have done today."

Noeggerath's rebuttal to such Procrustean denials of factual evidence was reservedly mild compared to one he might have made. Such cautious prophetic words that facts would eventually prevail were to be repeated a generation later (1903) under somewhat different circumstances, not in New York but in Berlin, by Ludwig Fränkel. The subject was not gonorrhea but the secretory function of the corpus luteum. The listeners were members, not of the American but of the German Gynecological Society. The reception, however, was similarly ultracritical, possibly because of the inability of the as yet unprepared minds to grasp an apparently revolutionary idea. The case for the Noeggeraths and the Fränkels was well stated in 1905 by William Stephenson, one-time Professor of Midwifery, University of Aberdeen, when he pointed out that his dissections of the cervix yielded results which differed widely from what had been implicitly accepted and was then taught. Observing that his teaching that close-felted connective tissue formed the chief bulk of the cervix fell on deaf ears, Stephenson[8] wrote, "New facts have been accumulating, but more thought has been spent in the endeavor to reconcile those with our old ideas, than to modify our ideas in accordance with the facts."

Rediscoverers

Recognition and remembrance are often matters of suitable occasion. Acknowledgment of an earlier idea is frequently made with the reservation that it was too novel for the time it was first stated and therefore not then acceptable. Early rising in the puerperium is a case in point. Recommended in 1773 by Charles White in his book, *Treatise on the Management of Pregnant and Lying-In Women,* it became a "new" therapy in our time because it dovetailed with current attitudes.

It is trite to believe that "there is nothing new under the sun," particularly in the light of modern medical technology, tagged isomers, antibiotics, and vaccines. But there are many examples in medicine to prove that not all that purports to be new is really so. Aristotle is credited with saying that "probably all art and all wisdom have already been full explored and again quite forgotten." This does not impugn the honesty of a later author. It is merely that the original description has been obscured by time. In this way, some good ideas are lost, or so casually stated as to be as good as lost. Many valuable observations remain sequestered, only to be restated in sharper fashion a generation or so later. The restatement—not, of course, known to be reiteration—glistens with newness. Examples of such rediscoveries may be found in two currently popular subjects.

Public Relations.—It is apparent on all sides of us, since we are exhorted in each journal picked up for leisure reading that the members of the medical profession are accused of neglecting the duties of citizenship and failing to be part of the community. This is also not new. It was treated editorially in 1898 by one of our most respected journals, as follows: "If the profession is to have any prospects at all, this subject in all its bearings cannot be too often nor too generally discussed in the medical press. We have been the first to endeavor to wake the profession from its long-time lethargy, to take its thoughts from mere money-grubbing to a rational view of its status in the community."[9] This extract could aptly appear in a current issue of any county medical journal.

Psychosomatic Gynecology.—Because psychiatry has grown tall during recent years, we have come to accept the thesis that a man is not merely a chemical factory but that he is also a thinking creature, a social person who affects his environment and is in turn affected by it. This has led to the tremendous current emphasis upon the need to evaluate the patient as a whole, considering not only the patient's illness but also her reaction to its therapy. Have we really discovered so-called "comprehensive gynecology"? Perhaps we are more appreciative of the need for it. At a meeting of this Obstetrical Society on June 2, 1898, the entire discussion was devoted to the effects mediated by the nervous system and behavior patterns upon the female generative organs. The most provocative of the papers of that evening, read by Francis X. Dercum,[10] was entitled, "On the Relation of the Great Neuroses to Pelvic Disease." If we substitute the word "psychoneurosis" for neurasthenia and hysteria, the two "great neuroses," Dercum's thesis is up to the minute. He emphasized the need for careful preoperative evaluation of the patient's personality, suggesting that the gynecologist is well advised to be wary of performing elective surgical procedures upon certain "unfavorably predisposed women." Dercum's conviction that better understanding of the individual woman would lead to better treatment of diseases peculiar to women was impressively and enthusiastically underscored by the 6 well-known gynecologists who discussed his paper.* To a man, they agreed upon the importance of

*E. E. Montgomery, E. P. Davis, George E. Shoemaker, Daniel Longaker, J. M. Baldy, and Charles P. Noble.

avoiding surgery in the psychoneurotic and subscribed to the guiding principle that preoperative study of the *whole* patient would decrease the number and severity of postoperatively encountered emotional storms. Current "research effort to gain understanding of the interrelationships of emotional and somatic factors in gynecological disease" is an extension in time of the earlier teaching of Dercum and others.

Comment

It must be here restated that the few sample threads drawn from the multicolored tapestry of our past have been chosen to "point a moral and adorn a tale." They illustrate the various shades of Time, to which this address is dedicated. The selections were made with deep respect for, but not necessarily devotion to, the past. In no sense is this recalling designed to be critical of those who seem now, in the glare of their future, to have been misguided. Their affirmations must be viewed in the proper setting, for the wisdom of winter is indeed madness in May. Take, for example, the function which Fallopius assigned to the uterine tubes, that of acting as chimneylike vents through which humors escaped. This hypothesis, though advanced for that time, was in keeping with the then accepted tenets of physiology. There is little doubt that our present glib explanations of the etiology of dysfunctional uterine bleeding will likewise raise derisive smiles in less than 400 years from now.

Nor is the purpose of this thesis to disparage the value of skeptical differences of opinion in molding usage in medicine. The several stories of those who, for a time, held back inevitable progress are related to emphasize the necessity of properly framing newly uncovered facts. They must either be accepted or exploded by penetrating criticism, and will then be superseded by more effective explanations. When such observations are followed by conflicting deductions, it should be realized that the interpretation must be wrong. Such an impasse requires solution by proper regrouping of the data and by the drawing of new inferences. Reconciliation is inevitable in a pluralistic world which is not made in a single pattern.

The sole intent of this presentation is to accent the significance of change and of tentative compromise, and to decry the rigidly opposing values, fixity of ideas, and unyielding dogma.

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THE ACTION OF PAPAIN AND BROMELAIN ON THE UTERUS

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Part I. Mucolytic Properties of Papain and Bromelain, Effect on Cervical Mucus

PAPAIN[1] is the crude, dried, powdered latex from the green fruit of the papaya tree *Carica papaya.* This name is also applied to partially purified preparations and to the first crystalline enzyme isolated from papaya latex by Balls and Lineweaver.[2] The crude preparations are also known by other names such as papayotin, caroid, and papoid, depending upon the manufacturer. Papain is an important commercial enzyme which has been used on a large scale since 1920. Papain also has many interesting and varied medical applications primarily as a proteolytic enzyme. It resembles pepsin and trypsin in its digestive activities but has a somewhat wider range of activities. Only one mention has been found in the literature regarding its use in gynecological procedures.[3]

Pineapple-stem bromelain is a new proteolytic enzyme mixture which is being produced on a pilot plant scale by some of the Hawaiian pineapple companies. In contrast to the classical fruit bromelin described in the literature,[4] stem bromelain is made from the juice which is squeezed from the stems of mature pineapple plants. It is similar to the bromelin of the mature pineapple fruit. This mixture is similar in its proteolytic action to papain but has the advantage of better color, odor, and availability.

This investigation was prompted by the need for a new technique to obtain more definitive x-ray pictures of the uterus. The thick, tenacious mucus that is so often seen in the cervical canal has always been an obstacle to critical study of the area. The mucus adheres closely to the wall of the canal and plugs the lumen, preventing the taking of radiographs which would demonstrate the anatomy of the canal accurately. As the radiopaque medium is injected, it forces a pathway through the mucus or the mucus is pushed before it. A variety of unusual patterns result, none of which are dependable. We began searching for a mucolytic agent which would clean the canal and allow the medium to make contact with the walls of the canal, permitting the taking of accurate radiographs. Kurzrock[3] used papain as a mucolytic agent in patients with chronic cervicitis and a thick mucopurulent discharge. Pregnancy resulted when he added 5 mg. of powdered papain to the specimen for artificial insemination. Traut[5] reported its use without harmful result as a gastric irrigant in searching for carcinoma of the stomach.

Description of Enzyme Preparation.—Several types of enzyme preparations were used in the investigation. In the early phase of the investigation, fresh, refrigerated latex* was used as a source of enzyme. Although this material had excellent activity, it had the disadvantages of being difficult to collect, required refrigeration, and gradually developed strong odors. Next, commercial papain was purified by dialysis against 0.001 M ethylenediamine tetraacetic acid to remove metals, then by further dialysis against distilled water, and then by freeze drying. The final product, which represented only about 20 per cent of the crude enzyme, had excellent activity and solubility (Table I).

Bromelain was prepared by fractionally precipitating the colloids in the juice from the stems of pineapple plants with ammonium sulfate or acetone and then dialyzing. The desired fractions were then freeze dried. Such preparations were white, free from odor, readily soluble in water, and had excellent proteolytic activity (Table I).

TABLE I. SOME PROPERTIES OF THE BROMELAIN AND PAPAIN USED IN THIS INVESTIGATION

	BROMELAIN	PAPAIN	FRESH PAPAYA LATEX
Milk clotting units (no cysteine)	4,200/Gm.	87/Gm.	1,200/Gm. solids
Milk clotting units (0.01 M cysteine)	4,300/Gm.	1,400/Gm.	1,200/Gm. solids
Protein digestion units*	20,000	310	-
Protein digestion units (0.01 M cysteine)*	59,000	56,000	-
Acid phosphatase units (mM/Gm.†)	1.2	Neg.	-

*Chow-Peticolas units.[6]
†mM = millimoles dinitrophenol liberated under standard conditions.

Stem bromelain is a mixture of many enzymes. It contains three proteolytic enzymes which are active over a range from pH 4.5 to pH 9.5. The enzymes acting at pH 6.8 and pH 8.5 contribute most of the proteolytic activity. Perhaps the most striking difference between stem bromelain and papain is in their response to cysteine and sulfhydryl poisons. Stem bromelain is quite active without cysteine activation and is only moderately affected by sulfhydryl poisons. Papain, on the other hand, was completely inhibited by N-ethylmaleimide and had poor activity unless it was activated by cysteine.

Laboratory Investigation.—Since one of the more obvious actions of both bromelain and papain on the uterus was the liquefaction of mucus, this action was investigated in the laboratory to determine the conditions which would give the optimum amount of liquefaction at physiologically acceptable pH ranges.

TABLE II. EFFECT OF pH ON THE ACTIVITY OF CYSTEINE-BROMELAIN SOLUTIONS IN REDUCING THE VISCOSITY OF BUFFERED HYALURONIC ACID SOLUTIONS

pH	CHECK 0.01 M CYSTEINE	HAVRU*/ML. BROMELAIN 2.94 MG. 0.01 M CYSTEINE	HAVRU/MG. BROMELAIN IN 0.01 M CYSTEINE
4.5	0.222	0	0
5.0	0.348	0	0
5.65	0.684	0.234	0.08
6.01	0.681	1.60	0.54
6.55	0.580	4.03	1.37
7.11	0.905	4.86	1.65

*HAVRU = Hyaluronic Acid Viscosity Reduction Units = $\frac{100\Delta V}{Vo\Delta t}$ where V = specific velocity at time t
ΔV = change in specific viscosity
Vo = initial specific viscosity
Δt = time interval over which viscosity was measured

*This material was supplied by Dr. G. D. Sherman of the University of Hawaii.

Hyaluronic acid was prepared according to the method of Humphrey[7] and was then freeze dried. For relative assay purposes the powder was dissolved in water, adjusted to the desired pH value with 0.1 M buffer, and then adjusted by dilution to a relative viscosity of approximately 3. Blank runs were made with the same amount of cysteine which was used in the enzyme.

As is evident from Table II, cysteine alone caused an appreciable reduction in the viscosity of hyaluronic acid. At pH values above 6, the combination of enzyme cysteine was quite effective. The activity of bromelain and papain was compared at pH 7.11 both with and without cysteine. Although both enzymes were activated by cysteine, bromelain showed considerable activity when used alone whereas papain was practically inactive (Table III).

TABLE III. COMPARISON OF BROMELAIN AND PAPAIN IN REDUCING THE VISCOSITY OF HYALURONIC ACID

ENZYME	HAVRU/MG. ENZYME	
	NO CYSTEINE	0.01 M CYSTEINE
Bromelain	1.23	1.67
Papain	0.036	0.33

The effectiveness of enzymatic degradation of hyaluronic acid was then compared with a nonenzymatic hydrolysis. The combination ascorbic acid–peroxide was much more effective in lowering the viscosity of the hyaluronic acid than was the enzyme (Table IV). If reduction in the viscosity of hyaluronic acid were the only desired effect, ascorbic acid–peroxide would be a more efficient agent than enzymes. However, since mucus is a combination of polyuronide material and protein, enzyme combinations such as bromelain and papain have an action which ascorbic acid–H_2O_2 alone does not have.

TABLE IV. EFFECTIVENESS OF ASCORBIC ACID (44 MG./ML.) AND 1.5 PER CENT PEROXIDE IN REDUCING THE VISCOSITY OF BUFFERED HYALURONIC ACID SOLUTIONS

pH	HAVRU PER ML.	MG. ASCORBIC ACID PER ML. 1.5 PER CENT H_2O_2	HAVRU PER ML.
4.5	60		
5.0	61	11	56
5.65	46	22	63
6.1	43	44	59
6.55	43	132	32
7.1	36		

The most effective ratio of ascorbic acid per milliliter of 1.5 per cent H_2O_2 appeared to be 27 mg. per milliliter 1.5 per cent H_2O_2, although the reaction was relatively insensitive to both pH and concentration of reagents.

Clinical Investigation.—Cervicohysterograms have been performed, so far as possible, at or near ovulation as shown on the temperature graph. The instruments and the technique were described by Hunter and Henry[8] in 1955. The primary salpingogram is performed in the usual manner using enough radiopaque medium* to cause spillage from the tubal ostia if possible. The cannula is then removed and the vagina filled with 50 to 60 c.c. of a solution of papain or bromelain. About five minutes is allowed for the action of the enzyme. The cannula is reapplied and the salpingogram repeated. The progress of the medium is followed by fluoroscopy and, at appropriate intervals, spot films are exposed.

*The radiopaque medium used in these studies was Salpix, supplied by the Ortho Pharmaceutical Corporation.

Results.—The radiographs taken after the use of this irrigating solution are of great interest. The anatomy of the cervical canal could be more easily and accurately visualized. Pseudo and actual space-occupying lesions could be more positively identified, and inflammatory changes of the canal and its glands could be diagnosed with accuracy. The activities of the cervix during these examinations were observed. At some future time we may be able to determine physiologically normal behavior.

Fig. 1.

Fig. 2.

Fig. 1.—Pseudo mass at the cervicouterine junction before papain.
Fig. 2.—After papain.

Fig. 1 shows a pseudo mass at the cervicoendometrial junction. This has the appearance of a polyp. Papain was used and Fig. 2 demonstrates the disintegration of the mass. This was obviously a mass of cervical mucus dislodged and forced upward by the medium as it was injected.

Fig. 3 illustrates the appearance of cervical polyps originating from the anterior longitudinal fold. Irrigation with papain failed to change the image except to clarify the picture.

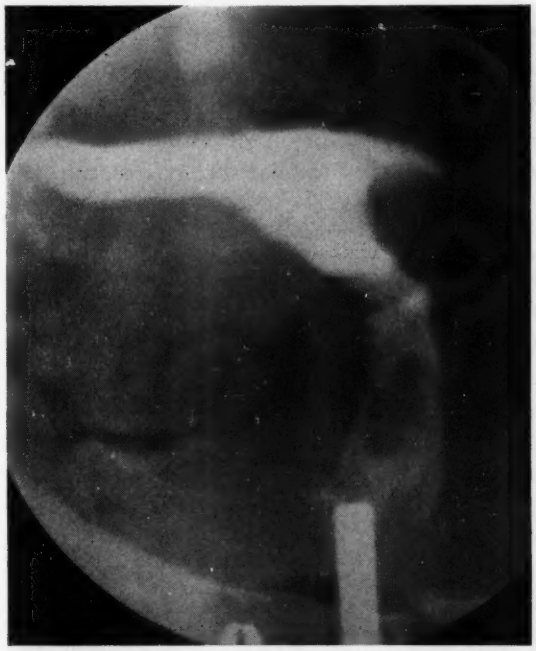

Fig. 3.—Space-occupying lesion of cervix which remained after papain.

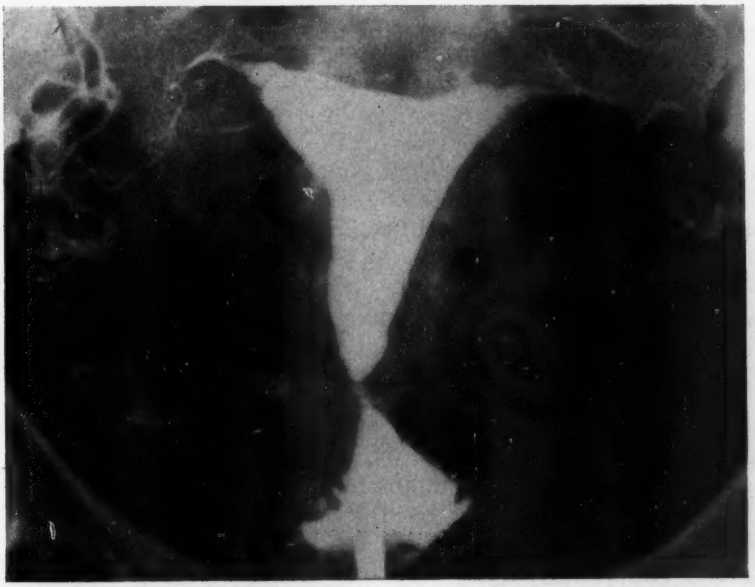

Fig. 4.—Endocervicitis. The shaggy appearance remained after irrigation with papain

Chronic endocervicitis has given us a consistent picture. The primary film often is completely normal. After papain has removed the mucus, the second x-rays show the infiltration of the medium into the glands with the resulting "shaggy" appearance seen in Fig. 4. Only those patients who have shown this shagginess on the secondary films have yielded tissue consistent with chronic cervicitis when surgery was performed.

Conclusions.—Two enzymes, papain and bromelain, are described and their mucolytic properties compared.

The technique of cervicohysterosalpingography using solutions of these enzymes is described and the results evaluated.

It is recommended that a solution of papain or bromelain be used as an adjunct in x-ray investigations of the cervix, uterus, and tubes.

Part II. The Use of Papain and Bromelain in Primary Dysmenorrhea

During the time when we were using papain in this study, it became apparent that some action other than the simple removal of the mucus was taking place. The following is a dramatic illustration of this effect. Fig. 5 shows the uterine shadow before the application of papain. Aside from anteflexion, this is essentially that of a normal cervix, uterus, and tubes. The lumen of the cervical canal is average in size, and the internal os is well shown. Fig. 6 shows the same uterus after irrigation of the canal with papain. The cervical canal, in particular, is greatly dilated. This enlargement and relaxation were so marked in some cases that a probable effect on dysmenorrhea was suspected.

A number of patients were selected who had so disabling a dysmenorrhea as to require narcotics for relief. They reported for examination and treatment as soon as cramping accompanied the flow. The hips were elevated on an examining table, a speculum inserted, and the vagina filled with a solution of papain or bromelain which was allowed to remain in the vagina for five minutes. If relief occurred, it was immediate and lasted for the duration of the period. One of these patients, a 28-year-old unmarried girl, has had disabling dysmenorrhea with every cycle. A dilatation and curettage was done in 1948 for cervical stenosis with relief for two and a half years. Gradually the pain returned to its former intensity and required the use of narcotics to allow her to continue at her job. A retained papain douche stopped the painful cramping within five minutes. The next menstrual period required no treatment. The third month was as painful as the first, and the relief just as dramatic.

A number of enzyme solutions have been used, some with equivalent results. Papain with cysteine in a buffer solution at pH 7.2 was used first. It was very effective but has the disadvantage that it must be mixed fresh each time; its activity diminishes with time. After mixture, it has a most disagreeable odor of organic sulfides released from the cysteine. Bromelain was then used in various buffers at varying pH. It was found that it is activated immediately by solution in a phosphate buffer at pH 5.5 and cysteine was unnecessary. After mixing, it is stable for up to two weeks if kept refrigerated. At present the solution is prepared as follows: A solution is made up so that each 50 c.c. of phosphate buffer will contain 0.075 Gm. of bromelain. A number of 2 ounce bottles are filled and the solution freeze dried. When needed,

water is added and the material is ready for use. When cramping accompanies flow, the materials are mixed and injected slowly into the vagina by pouring directly from the 2 ounce bottle or using an infant's rectal syringe. The patient remains in the Trendelenburg position for five minutes.

Ideally the material should be used as soon as cramping appears with the onset of flow. When used later, some lateral adnexal soreness remains and is unrelieved for a few hours. When relief occurred, there was no recurrence of pain during the remainder of the menstrual flow. Only one complication has been encountered so far. Occasionally the relaxation of the cervix has been so great that all the accumulated material within the uterus pours out, giving the patient the impression of flooding. This has lasted only a few moments and in no case has the quantity been truly excessive.

Fig. 5.

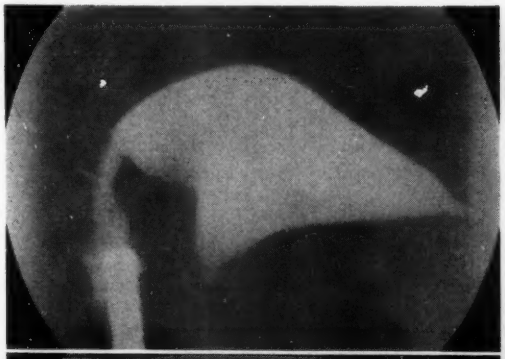

Fig. 6.

Fig. 5.—Normal uterus before papain.
Fig. 6.—Normal uterus after papain.

Sixty-four patients have been treated, 40 of whom obtained immediate relief. The remaining 24 obtained poor to fair results and were classified after examination as having secondary dysmenorrhea. The results so far have been best in the teen-agers, young nulliparas, and a few older patients without concurrent gynecologic disease. Only fair to poor results have been obtained in the secondary[9] or congestive [10] dysmenorrhea. The reasons for this are quite obvious. Diseases of the cervix such as cervicitis, strictures of inflammatory origin, and cervical polyps are rare in the young. Polyps of the endometrium large enough to act as ball valves, endometritis, adenomyosis,

Chronic endocervicitis has given us a consistent picture. The primary film often is completely normal. After papain has removed the mucus, the second x-rays show the infiltration of the medium into the glands with the resulting "shaggy" appearance seen in Fig. 4. Only those patients who have shown this shagginess on the secondary films have yielded tissue consistent with chronic cervicitis when surgery was performed.

Conclusions.—Two enzymes, papain and bromelain, are described and their mucolytic properties compared.

The technique of cervicohysterosalpingography using solutions of these enzymes is described and the results evaluated.

It is recommended that a solution of papain or bromelain be used as an adjunct in x-ray investigations of the cervix, uterus, and tubes.

Part II. The Use of Papain and Bromelain in Primary Dysmenorrhea

During the time when we were using papain in this study, it became apparent that some action other than the simple removal of the mucus was taking place. The following is a dramatic illustration of this effect. Fig. 5 shows the uterine shadow before the application of papain. Aside from anteflexion, this is essentially that of a normal cervix, uterus, and tubes. The lumen of the cervical canal is average in size, and the internal os is well shown. Fig. 6 shows the same uterus after irrigation of the canal with papain. The cervical canal, in particular, is greatly dilated. This enlargement and relaxation were so marked in some cases that a probable effect on dysmenorrhea was suspected.

A number of patients were selected who had so disabling a dysmenorrhea as to require narcotics for relief. They reported for examination and treatment as soon as cramping accompanied the flow. The hips were elevated on an examining table, a speculum inserted, and the vagina filled with a solution of papain or bromelain which was allowed to remain in the vagina for five minutes. If relief occurred, it was immediate and lasted for the duration of the period. One of these patients, a 28-year-old unmarried girl, has had disabling dysmenorrhea with every cycle. A dilatation and curettage was done in 1948 for cervical stenosis with relief for two and a half years. Gradually the pain returned to its former intensity and required the use of narcotics to allow her to continue at her job. A retained papain douche stopped the painful cramping within five minutes. The next menstrual period required no treatment. The third month was as painful as the first, and the relief just as dramatic.

A number of enzyme solutions have been used, some with equivalent results. Papain with cysteine in a buffer solution at pH 7.2 was used first. It was very effective but has the disadvantage that it must be mixed fresh each time; its activity diminishes with time. After mixture, it has a most disagreeable odor of organic sulfides released from the cysteine. Bromelain was then used in various buffers at varying pH. It was found that it is activated immediately by solution in a phosphate buffer at pH 5.5 and cysteine was unnecessary. After mixing, it is stable for up to two weeks if kept refrigerated. At present the solution is prepared as follows: A solution is made up so that each 50 c.c. of phosphate buffer will contain 0.075 Gm. of bromelain. A number of 2 ounce bottles are filled and the solution freeze dried. When needed,

water is added and the material is ready for use. When cramping accompanies flow, the materials are mixed and injected slowly into the vagina by pouring directly from the 2 ounce bottle or using an infant's rectal syringe. The patient remains in the Trendelenburg position for five minutes.

Ideally the material should be used as soon as cramping appears with the onset of flow. When used later, some lateral adnexal soreness remains and is unrelieved for a few hours. When relief occurred, there was no recurrence of pain during the remainder of the menstrual flow. Only one complication has been encountered so far. Occasionally the relaxation of the cervix has been so great that all the accumulated material within the uterus pours out, giving the patient the impression of flooding. This has lasted only a few moments and in no case has the quantity been truly excessive.

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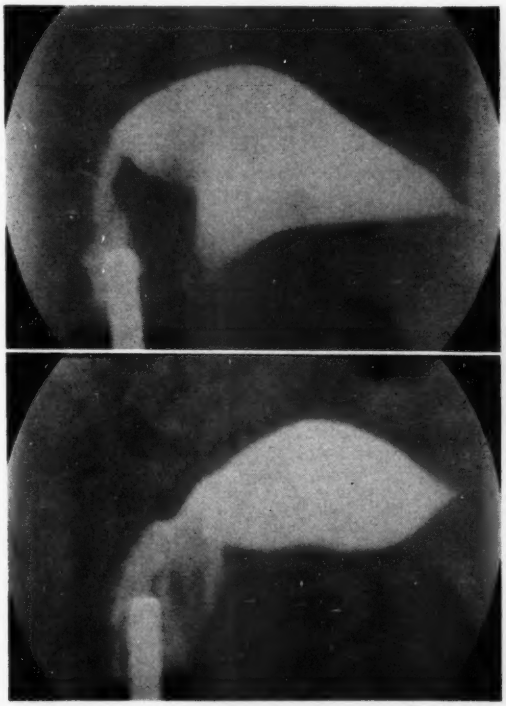

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endometriosis, and parametritis are unusual. Tubal disease is more uncommon, and ovarian disorders capable of producing pain at flow are infrequent. These patients receive relief only if spasm of the cervix is a principal component of the total disorder.

Patients of all types have been treated and offered the materials for home treatment for one occasion only, if no relief has been obtained. Those patients whose results have been less than good have been examined more completely to determine, if possible, any underlying disorder or disease.

The evaluation of the amount of pain and disability of each individual has always been a difficult problem for all of us. Those who concern themselves with the condition of the great numbers of women in industry have an enormous task. How much conscious and unconscious malingering and absenteeism take place on the basis of dysmenorrhea is a hard question to answer. The use of papain and bromelain may be of some assistance to those investigators.

We wish to express our appreciation to Mrs. Ann Madsen of Queen's Laboratory for preparation of the enzyme solution.

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THE ACTION OF PAPAIN AND BROMELAIN ON THE UTERUS

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HONOLULU, HAWAII

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Part III. The Physiologically Incompetent Internal Cervical Os*

REPEATED or habitual abortion has always been a most distressing problem to the obstetrician and gynecologist. Defects of the internal cervical os may play some part in the early abortions, but it is felt that they play a principal role in the loss of pregnancies in the second trimester and later. Many explanations have been given, but there are still numerous patients who lose their pregnancies, although examination had shown each to have a normal fetus and apparently a normal implantation, as evidenced by early sacculation. These patients appear with a widely dilated external cervical os and bulging membranes, to be followed by the gentle oozing of the fetus and amniotic sac through the cervical canal with loss of the pregnancy. In 1950 Lash and Lash[1] described the condition and a method of repair which was further elaborated by Lash[2] and his associates in 1953. Palmer and Lacomme[3, 4] discussed the problem and offered a method of investigation and repair. In 36 cases of habitual abortion investigated by hysterosalpingography, Palmer[5] found: 5 patients with fibroids, 7 with malformations with significant bicornuate uterus, 7 with hypoplasia (4 with discrete bicornuate fundus) and 3 with associated gaping of the isthmus, 2 with hyperanteflexion and hypercontractility, 2 with hypercontractility alone, and 6 with gaping of the isthmus alone. In 6 the findings were normal. He states, "The possible causation factors of this gaping of the isthmus are . . . traumatic (overdilatation), congenital, and functional (nervous)."

The commonest form is usually caused by injury, such as placenta previa, lacerations of delivery, or too enthusiastic curettage. This is easily demonstrated by the method of Riazzi-Palmer,[4] or that of Lash and Lash,[1] or by the use of a revised cannula and cervicosalpingography as demonstrated by Hunter and Henry.[6] The single or multiple defects are definitely located and the field of repair can be accurately defined by the latter method. Repair by Lash's method of imbrication results in marked success in this particular group. Danforth who first objected to the terminology now agrees that it is logical and that the entity does exist. We would like to call this entity the structurally incompetent os.

The congenital type, which we have found to be the least common in occurrence, is always associated with primary habitual abortion. None of these

*The radiopaque medium used in these studies was Salpix, supplied by the Ortho Pharmaceutical Corporation.

patients have delivered a full-term infant. The gaping of the os is very similar to that of the functional incompetence. No localized outpouching as of an unhealed injury can be found.

We have found another form of incompetency which is not demonstrable by the usual means and apparently is of a different origin. The method of cervicohysterosalpingography was published in 1954 by Hunter and Henry, and the use of the enzymes such as bromelain and papain was demonstrated

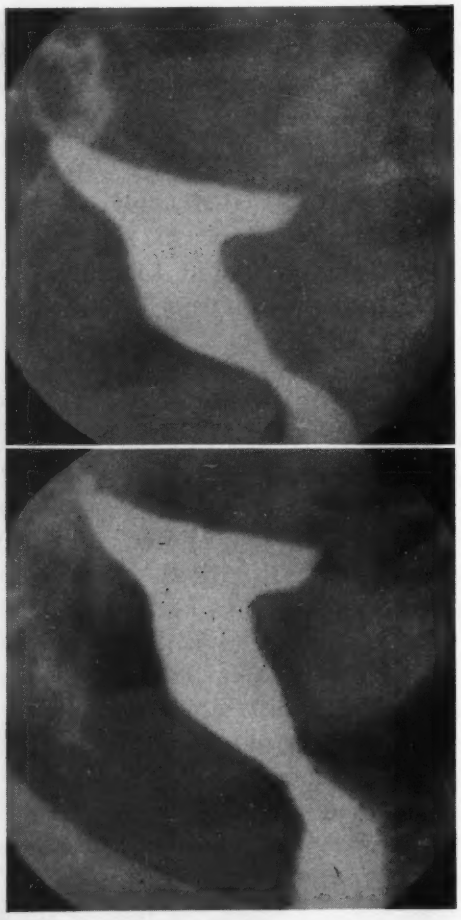


Fig. 1.—Normal uterus before and after papain.

at that time. These enzymes were used first to remove excessive cervical mucus. Observations following its use demonstrated that pseudo and actual space-occupying lesions could be more positively identified and inflammatory changes of the canal and its glands could be visualized with greater accuracy. The activities of the cervix were observed during these examinations.

It soon became apparent that some action other than the simple removal of mucus was taking place. The cervical and uterine shadow was so markedly changed that we were sure that some relaxing effect was obtained. The cervical canal, in particular, was greatly dilated. Fig. 1 shows an example

of this enlargement. Relaxation was so marked in some cases that a probable effect on dysmenorrhea was suspected. These studies have been reported by Hunter, Henry, and Heinicke.[7]

This relaxation has occurred to varying degrees in practically all of the patients examined, but in this series all but a few patients have retained the

Fig. 2.—Structurally incompetent internal os. (From Hunter and Henry: Fertil. & Steril. 6: 68, 1955.)

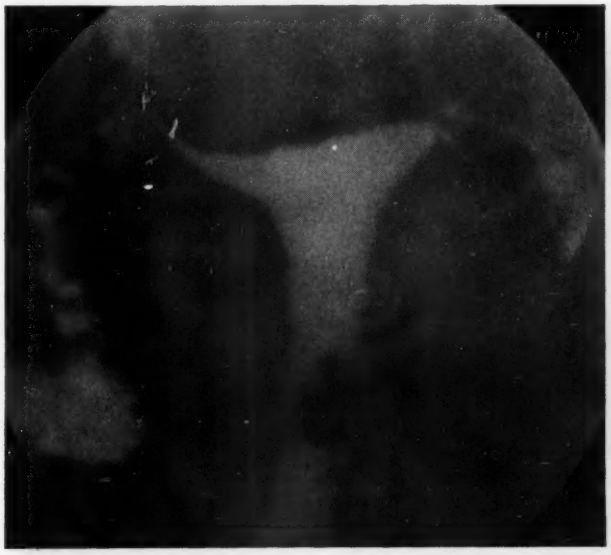
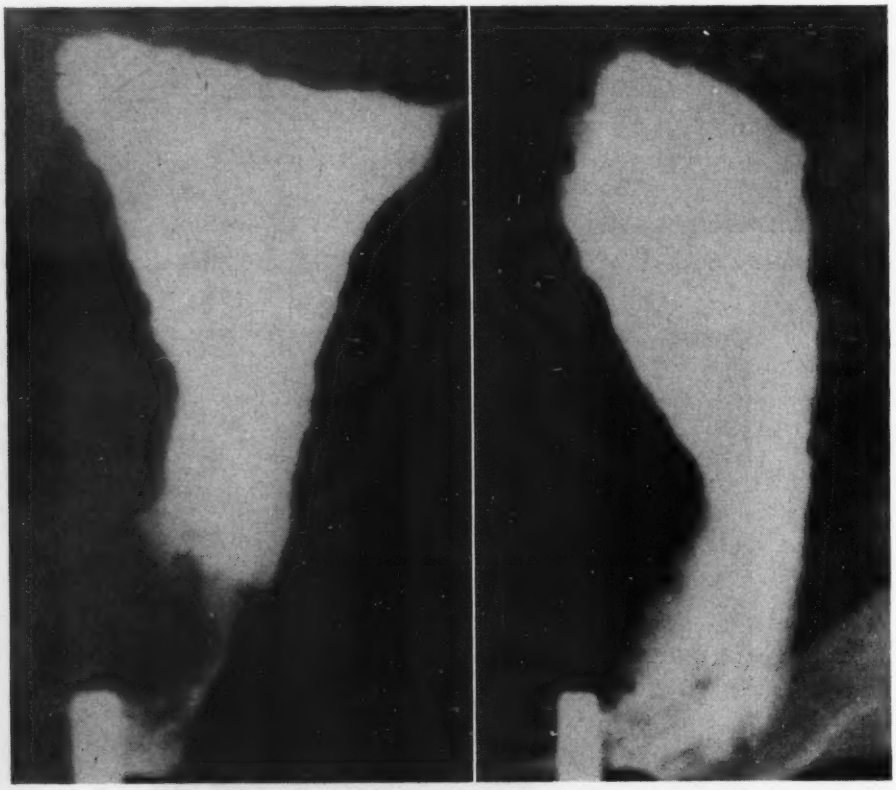


Fig. 3.—Structurally incompetent internal os and a polyp of the cervical canal.

usual contour of the uterocervical shadow. Fig. 2 shows the usual structurally incompetent os as demonstrated on the primary salpingogram before the use of papain. There is no difficulty in making this diagnosis. It adequately explains this woman's failure to retain her pregnancies for any length of time.

The next illustration, Fig. 3, is that of a patient who has never delivered a full-term infant, and, as you see, the cervical canal has a uniform broad caliber throughout its entire length with no evidence of an internal os. The diameter of the cervical canal is many times greater than that of the normal. This was unchanged by the use of papain and probably was congenital or embryological in its origin.

Fig. 4, *A*, shows an apparently adequate internal cervical os and a normal uterine shadow. Fig. 4, *B*, shows the same uterus after irrigation of the cervix with papain. The uterine shadow has enlarged in all directions, and the region of the internal os is no longer clearly defined. The constriction representing this muscular activity is gone, and the grossly dilated cervical canal merges smoothly into the endometrial cavity. The similarity between this picture and that of the structurally incompetent os is striking.



A. *B.*

Fig. 4.—*A* and *B*, Physiologically incompetent os before and after papain.

This patient demonstrates what we call a physiologically incompetent internal cervical os. The canal appears normal on the first cervicohysterosalpingogram. After irrigation with papain, the canal relaxes, its original contour disappears, and it assumes the appearance of a large cylinder. The cervix dilates in an abnormal way. The change produced by these enzymes presumably mimics the dilatation of pregnancy, resulting in incompetency of

the internal os. All our patients showing this relaxation of the internal os with papain have lost three or more pregnancies between 12 and 20 weeks. Once having aborted during the middle trimester, none of them have subsequently carried a pregnancy to term. Whether repair of this defect will enable any of them to carry their pregnancies to term remains to be seen.

Internal pressure within the amniotic sac produces dilatation and enlargement of the uterus. If the internal os remains closed, the pressure is applied uniformly to the entire internal surface of the uterus, according to Pascal's law. In the normal pregnant uterus, the internal os is tightly closed, and the sac cannot bulge into the cervical canal. If the internal os is open, the pressure of the amniotic fluid pushes the sac into the cervical canal. The same pressure which is applied against the lining of the muscular uterus is then applied to the walls of the cervical canal resulting in further dilatation and further bulging of the sac. The muscular force of the continually contracting uterus is transmitted to the cervix and further pouching of the sac occurs. Eventually these patients are seen with bulging membranes and a patent external os. The pregnancy is soon lost.

Five of the patients in this series became pregnant again before any type of repair could be effected. They all aborted at from 15 to 23 weeks with repetition of their former chain of events. Three of these 5 had excessive bleeding and evidence of retained secundines and were brought to dilatation and curettage. At operation the cervices presented an entirely different picture from that seen in the average and in the structurally incompetent os.

The cervix was widely dilated, very soft, and appeared as a cuff of tissue about 1 cm. in thickness. This measurement was uniform throughout the cervical circumference and extended into the uterine cavity. There was no ridge at the internal os as usual. The curette could be passed from the fundus to the external os without a trace of tissue obstruction. The internal os had completely disappeared.

Three of the patients demonstrating these changes have been operated upon. The repairs have been done by the Lash method. Two of the patients have subsequently become pregnant only to repeat the original chain of events. The cervices have been unimproved by the surgical procedures. While the repair by this method has served very well for those who demonstrate a structurally incompetent os, it is not sufficient re-enforcement for the physiologically incompetent one. Subsequently we have attempted a different type of repair, the results of which will be published at a later date.

We are now investigating all patients who have lost pregnancies beyond 12 weeks to determine whether this is a common finding. Ten patients to date, all those examined with such a history, have shown this phenomenon. In no case without this history of pregnancy loss beyond 12 weeks has such a change been shown. The ordinary lacerated canal or other variation in no way approaches this broad change. The enzyme-induced dilatation is apparently a specific means of demonstrating the physiologically incompetent os.

We wish to express our appreciation to Mrs. Ann Madsen of Queen's Laboratory for preparation of the enzyme solution.

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Case Reports, New Instruments and Methods

CONGENITAL ATRESIA OF THE LOWER THIRD OF THE VAGINA WITH CONCEALED HEMATOCOLPOS*

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THE weight of investigative and clinical evidence indicates that the vagina is of dual origin, the upper two thirds deriving from the caudal portion of the fused Müllerian ducts and the lowermost third from the urogenital sinus.

Reports of congenital absence of the entire vagina are not infrequent. Such agenesis is usually associated with absence or anomalous development of the uterus and Fallopian tubes, and represents developmental failure of both the Müllerian duct system and the urogenital sinus anlage of the lower portion of the vagina. Absence of the Müllerian system alone (Fallopian tubes, uterus, and upper two thirds of the vagina), the lower one third of the vagina being normal, has been described.[1] That the reverse may occur, the upper two thirds of the vagina developing independently of the lower one third, has been doubted.[2] Several such instances have, however, been reported.[3] This communication presents an additional example.

Case Report

Miss M. A. E. (No. B30767), aged 16, was admitted to the Southern Division of the Albert Einstein Medical Center on May 28, 1954.† She had complained for a year of episodes of dull low back pain, recurring at intervals of a month or more and lasting one or two days. She had never experienced menstrual flow. There was nothing else in her past history of consequence.

Physical examination showed an apparently well white girl, endowed with normal feminine appearance, manner, and voice. There were no endocrine stigmas. No positive findings were uncovered except for the presence of a tense round mass barely palpable above the symphysis pubis, which was not tender. Gynecologic examination showed an average quantity and normal distribution of pubic hair. The external genitals were normal in appearance except for an imperforate hymen which showed no bulging. The uterus and adnexa were not palpable rectally, but in their place was the aforementioned mass. Bimanually, it presented as a globular, tensely cystic tumor approximately 12 cm. in diameter.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Jan. 5, 1956.

†The patient was treated through the courtesy of Dr. Hannah E. Seitzick-Robbins, Trenton, N. J.

The patient's blood count was within average range and there were no abnormal findings in a voided specimen of urine.

Operation was performed on May 29 with the patient in the lithotomy position under Pentothal-nitrous oxide anesthesia. An indwelling catheter was placed in the bladder; a second landmark was provided by the surgeon's finger kept in the patient's rectum. The "hymenal membrane" proved to be fibrous tissue of some thickness. It was perforated by means of a 15 gauge needle which was advanced slowly for a distance of 4 cm. before a flow of dark, syrupy blood was obtained. With the needle in place as a guide, the fibrous cord representing the uncanalized lower third of the vagina was excised, allowing approximately 800 c.c. of old blood to escape. Examination of the hematocolpos cavity after it had been irrigated with physiologic saline solution showed it to be the markedly dilated upper two thirds of the vagina lined by typical mucosa. The cervix appeared normal and admitted a sound to a depth of 5 cm. The uterine body was anterior, and of normal size and contour (Fig. 1).

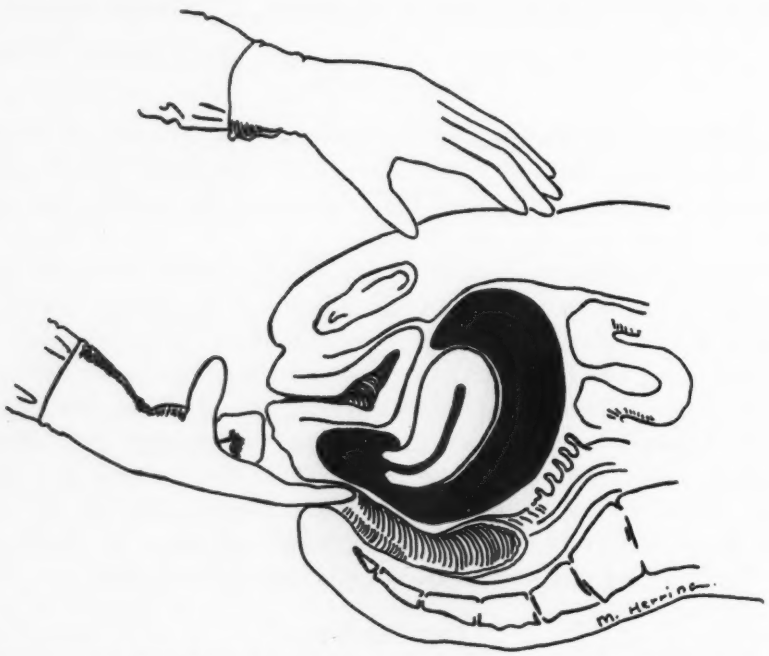

Fig. 1.—Schematic drawing showing absence of lower third of vaginal lumen and presence of huge hematocolpos.

The lower margin of the vaginal wall, mobilized by means of scissors, was drawn downward and attached to the edge of the hymenal ring with interrupted sutures of No. 4-0 atraumatic chromic catgut. A small gauze sponge was placed in the vagina and the indwelling catheter left in the bladder, both of which were removed after 24 hours.

The patient was discharged on the second postoperative day, having experienced an entirely satisfactory course. No hormone therapy, douches, or vaginal dilatations were prescribed. Periodic follow-up examinations during the succeeding 18 months showed the patient to have a vagina of adequate depth and caliber. Her menstrual function has been normal.

Comment

Some authorities believe that the entire vagina is derived from the fused lower portion of the Müllerian ducts.[4] Others contend that the upper two thirds of the vagina is of Müllerian origin, the lower third being formed

from the conjoined terminal end of the Wolffian ducts.[5] Vilas[6] attributed development of the whole vaginal tube to canalization of a solid cord growing in a cephalad direction from the urogenital sinus. A critical review of the principal concepts of vaginal development was presented by Koff,[7] whose dissections showed the lower part of the vagina to be derived from the urogenital sinus and the upper part from the fused lower portion of the Müllerian ducts. According to Koff, the solid tips of the Müllerian ducts, having burrowed caudally through the genital cord mesenchyme, fuse and

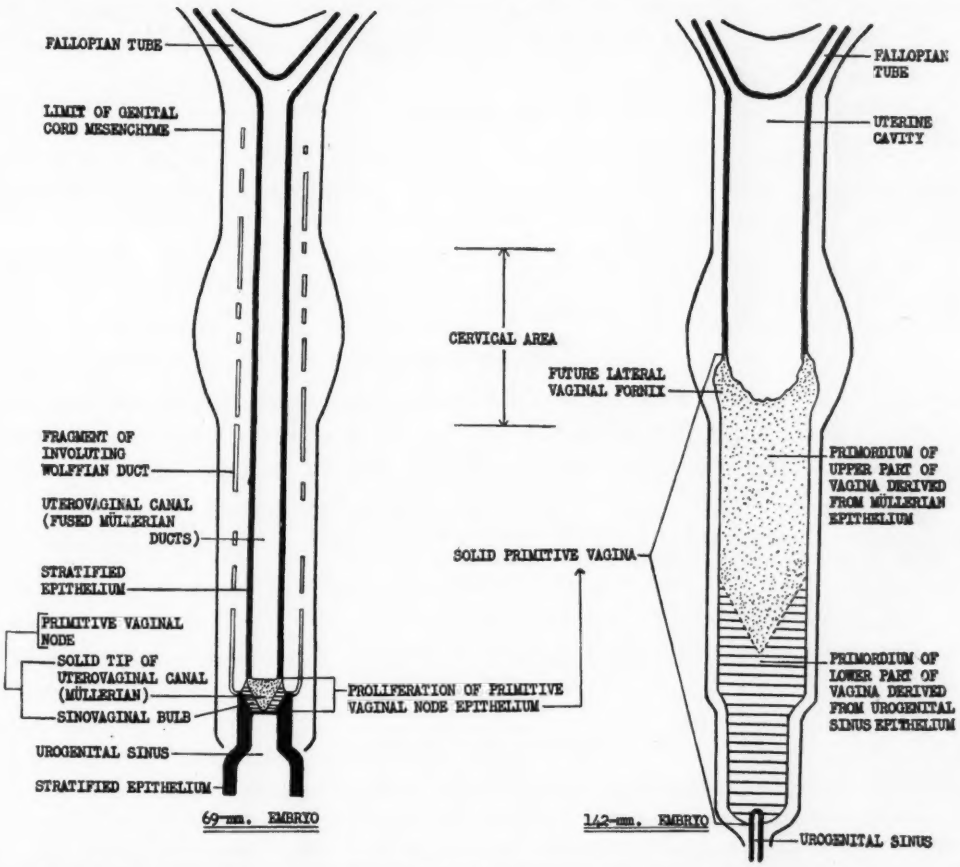

Fig. 2.—Diagrammatic representation of development of the primitive vagina. The sinovaginal bulbs, paired evaginations from the posterior wall of the urogenital sinus, solidify by epithelial proliferation and join with the similarly solidified tip of the fused Müllerian ducts to form the primitive vaginal node. Upward growth of this dual structure produces the solid primitive vagina, later canalized by a process of central degeneration and desquamation. The separate components, Müllerian and urogenital sinus, are not, in actuality, distinguishable from one another at the depicted 142 mm. stage. Histologic and morphologic differences apparent in both earlier and later stages indicate the dual origin of the vagina. (Modified from Koff: Contrib. Embryol. 24: 61, 1933.)

advance to the posterior wall of the urogenital sinus where an invagination, the Müllerian tubercle, appears at the area of contact. Obliteration of the tubercle then occurs as the two sinovaginal bulbs, bilateral posterior evaginations of the urogenital sinus, solidify, grow by epithelial proliferation, and join the similarly solidified tip of the fused Müllerian ducts (uterovaginal canal) to form the primitive vaginal node. Subsequent proliferation of the

epithelium upward from the primitive vaginal node results in solidification of the uterovaginal canal as far as the site of the future vaginal fornices. Thus, the lower portion of the primitive vagina, the solid vaginal cord, develops from the sinovaginal bulbs of the urogenital sinus and the upper part from the Müllerian epithelium of the uterovaginal canal (Fig. 2). Finally, vaginal canalization takes place through a process of central degeneration and desquamation.

It is suggested that the anomaly herein described, representing an instance of either agenesis or failure of canalization of that portion of the embryonal vaginal cord derived from the urogenital sinus, is best explained by the view of Koff.

Summary

1. The clinical details of a case of congenital absence of the lower third of the vagina with concealed hematocolpos, including its operative management, are herewith reported.

2. It is averred that the occurrence of such an anomaly supports the theory of dual origin of the vagina.

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MASCULINOVOBLASTOMA: AN ADRENAL CORTICAL TYPE OF TUMOR OF THE OVARY

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SECRETING tumors of the ovary have the remarkable "Jekyll-Hyde" ability to accentuate female traits by their production of estrogen-like steroids or to induce masculine features through their production of androgen-like compounds. The latter group of functioning tumors which cause masculinization include the arrhenoblastoma, dysgerminoma, hilum-cell tumor, and the rare masculinovoblastoma. The term "masculinovoblastoma" was introduced by Rottino[1] in 1939 to apply to those masculinizing ovarian tumors which microscopically resemble the adrenal cortex.

Twenty-nine verified cases of masculinovoblastoma have been reported. Iverson[2] reviewed 15 cases in 1947. Merivale[3] culled 9 more from the literature and added one of his own in 1951. Patil[4] reported 2 and Michaelson[5] and Rhoads[6] each reported a case.

We shall report the following case of a masculinovoblastoma for which urinary 17-ketosteroids and "pregnanediol complex"* were determined. Only a few of the more recent reports record the 24 hour urinary 17-ketosteroid excretion, and Merivale's report is the only case accompanied by "pregnanediol complex" excretion values.

Case Presentation

Mrs. T. M., a 29-year-old woman, born in Italy, complained of progressively developing hirsutism of one year's duration, hoarseness of six months, and decrease in the size of the breasts and amenorrhea of three months' duration. There was no change in sexual potentia. The patient had been married for 9 years, had been pregnant once, and had a 5-year-old son at the time of examination. She had been examined by one of us (H. M. W.) seven months prior to the present complaints and found to be normal. Previous history disclosed no other contributing facts. Photographs of the women in the patient's immediate family showed no abnormal hirsutism.

Examination disclosed a well-proportioned, attractive young woman with a hoarse voice. There was mild acne of the face and back. The hair distribution showed a male type of escutcheon, fuzz on the upper lip and chin, and a more moderate hair development on the lower abdomen and thighs. The blood pressure was 130/60. The thyroid was not palpable. The breasts were small but well formed. The clitoris was of normal size.

*The analysis for "pregnanediol complex" was performed in accordance with the technique of Sommerville[7] which actually measures pregnanediol and pregnanetriol.[8] Because the analysis determines both, the term "pregnanediol complex" is used.

No abnormality was demonstrated in roentgenograms of the pituitary fossa, and in the intravenous pyelogram and presacral air insufflation to outline the suprarenal areas.* The blood count and hematocrit, glucose tolerance test, serum sodium, potassium, and carbon-dioxide combining power were within normal limits.

After a 24 hour urine specimen was analyzed for 17-ketosteroids, cortisone was administered intramuscularly, 400 mg. per day, for four days. On the fourth day urine was obtained for 17-ketosteroid determination. The 24 hour excretion of urinary steroids† is given in Table I. Before further steroid studies could be performed and because of clinical urgency, the patient was operated upon.

TABLE I. TWENTY-FOUR-HOUR URINARY EXCRETION OF STEROIDS

	FIRST	DURING CORTISONE	1 MONTH POSTOPERATIVELY	8 MONTHS POSTOPERATIVELY	NORMAL VALUES	
17-Ketosteroid	121 mg.	63 mg.	12 mg.	8 mg.	5-17 mg.	
"Pregnanediol complex"	46 mg.				1 mg. (early phase of cycle)	15 mg. late phase of cycle)

Fig. 1.—Right ovarian tumor.

Through a lower left vertical rectus incision, extending from below the umbilicus to just above the symphysis pubis, the lower abdominal cavity was opened under general anesthesia. About ½ pint of straw-colored fluid was found in the pelvis. A right salpingo-oophorectomy, wedge biopsy of the left ovary, and appendectomy were performed. The right ovary was replaced by a yellowish-white, irregularly shaped tumor, which was freely movable and about the size of a tennis ball, resting on the right side of the posterior pelvic wall. When the tumor was incised, following its removal, a broad, scalloped,

*Dr. Benjamin Salway, Department of Surgery of St. Francis Hospital, performed the presacral air insufflation.

†The hormone analyses were carried out in the Division of Endocrine and Cancer Research of Jefferson Medical College.

bright-yellow area about 1½ cm. in width was seen at least 2½ cm. beneath its capsule (Fig. 1). The tumor, at the periphery of the scalloped yellow area, was soft, which fact may have accounted for the lack of preoperative pelvic findings. On repeated section, the cut surfaces showed a circular scalloped band of orange-colored tissue which grossly resembled adrenal gland.

The microscopic examination* (Fig. 2) showed a section of ovarian tumor. Its outer wall contained some compressed ovarian tissue recognized by ovarian stroma and the presence of a small follicle lined by typical follicular cells. There was mild edema of the stroma as well as compression. The center of the lesion was separated from the normal ovarian stroma by very loose fibrous tissue within which were observed thick-walled blood vessels and a considerable amount of frank blood. The tumor itself was composed of large sheets of cells. These appeared to have a very pale, slightly vacuolated cytoplasm and contined small amounts of granular material. The nuclei in most instances were centrally placed and appeared very small and pyknotic. The cell outlines were very distinct and easy to discern. They appeared in many respects to be mirror images of those seen in normal adrenal tissue. No evidence of malignancy was noted within the tissue.

The pathological diagnosis was masculinovoblastoma of the right ovary.

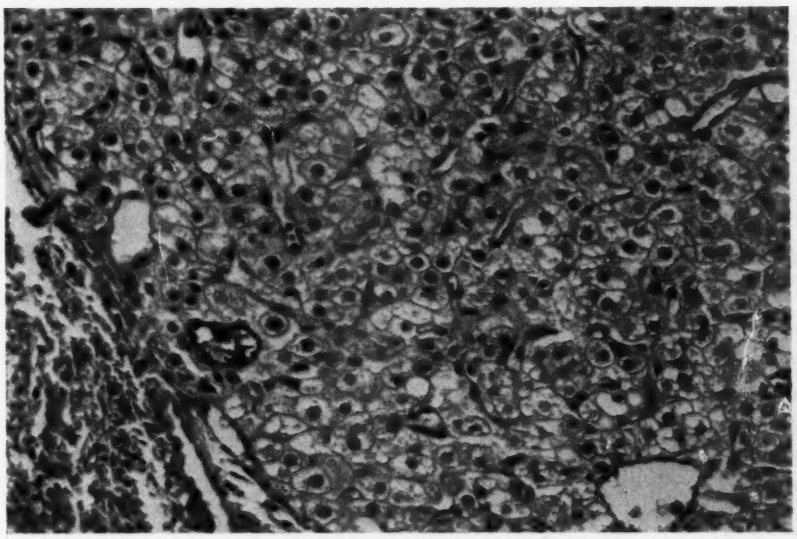

Fig. 2.—Microscopic enlargement of tumor cells. (×400; reduced ¼.)

Eight months later, the patient was examined and found to have a marked diminution in hirsutism, enlargement of the breasts to normal size, and decrease in extent of the acne. Her periods had become regular but the hoarseness persisted unchanged. The 17-ketosteroid excretion was 8 mg. per 24 hours.

Comment

At present, unless one can palpate a pelvic mass or visualize an adrenal tumor by air studies, there is no means by which the examiner can predict before operation whether a particular case of masculinization is due to an abnormality of the ovary or of the adrenal cortex. No combination of signs and symptoms can be used to designate either the ovary or the adrenal as the site of the masculinizing tumor.[9] The practical importance of knowing the

*We are grateful to Dr. Solomon Weintraub, Pathologist, St. Francis Hospital, for the pathological material included.

location of the trouble preoperatively is evident. Therefore it is important to document cases of masculinovoblastoma, not only because of their rarity and interest as "adrenal tumors" of the ovary, but also because additional observations in these cases may make future recognition simpler. With added knowledge, the uncertainty of the site of the tumor at laparotomy and the occasional need for multiple surgical procedures may be eliminated. In addition, further light may be shed on the problem of hirsutism in general.

Presented with a case of masculinization, several diagnostic avenues must be explored. Is the symptom complex simply a constitutional defect? Can the pituitary be absolved of responsibility? If the adrenal cortex is responsible, is it hyperplasia or tumor, malignant or benign, left or right adrenal? Or is the ovary at fault?

The decision in a particular case that a pathological masculinizing syndrome may exist is the first and sometimes the most difficult step. This is so because, once such a conclusion is reached, the physician must spend time, effort, and the patient's money looking for the aberration. The justifiable reluctance of most physicians to investigate such a case is evident if one notes the delay from onset of symptoms to treatment in these instances. A review of the literature showed that most patients suffered three to five years without treatment, and one patient suffered from a secreting tumor for 32 years until it was investigated.[3]

Pituitary hypersecretion usually does not cause pure masculinization or defeminization as seen in this instance. However, a hypersecretory adrenal cortex could produce such a picture. The observed normal urogram and perirenal x-rays combined with an increase in excretion of 17-ketosteroids (121 mg.) and of "pregnanediol complex" (46 mg.) suggested adrenal cortical hyperplasia. However, in adrenal hyperplasia, ideally, one would expect an elevated 17-ketosteroid, which is depressed to normal values during cortisone administration, and an increased excretion of "pregnanediol complex."[8]

Actually, neither the pituitary nor adrenal was at fault in this instance, for the patient had an "adrenal-cortical type" of secreting tumor of the ovary, a masculinovoblastoma. Although there are exceptions, Kepler[9] felt that an increased 17-ketosteroid excretion is typical of this tumor. Merivale[3] found an increased "pregnanediol complex" excretion as we did. Since the period of cortisone administration in this case was so short and since the results of 17-ketosteroid excretion during this period were not clear-cut, we feel that no conclusion is warranted from the scant data. The decrease in 24 hour urinary excretion from 121 mg. to 63 mg. of 17-ketosteroid could be a biological variation in day-to-day excretion of the steroid rather than the result of cortisone suppression of the adrenal cortex.

The excessive production in the urine of pregnanediol and especially pregnanetriol has been considered to be characteristic of cases of adrenal cortical hyperplasia with virilism.[8] This finding has led to the belief that the basic defect in this disease is a relative inability of the adrenal to hydroxylate a C-21 steroid at the 11β and 21 positions.[10] As a result of this aberration

larger quantities of a virilizing,[11] but incomplete adrenal steroid, probably 17-hydroxyprogesterone, are produced. This substance is thought to be an intermediary in the synthesis of compound F in the adrenal gland.[12] However, this compound fails to inhibit the pituitary ACTH production to an adequate extent and thus permits the continuing production of ACTH with the resultant adrenal hyperplasia.[10] The hyperplastic adrenal cortex eventually produces enough of the physiologic pituitary inhibitor, 17-hydroxycorticosterone or compound F, to bring the production of ACTH to a steady, although excessive, state. In the interim, abnormally large quantities of 17-ketosteroid, the probable metabolic end product of the aforementioned 17-hydroxyprogesterone, are excreted in the urine.[10]

In this case of a masculinovoblastoma, the excessive urinary steroid excretion, 17-ketosteroid and "pregnanediol complex," coupled with the clinical syndrome and microscopic pathology, recalls cases of virilism due to adrenal cortical hyperplasia. Whether the pathological physiology is the same as in adrenal hyperplasia cannot be answered at this time. However, the similarity in clinical picture and in urinary steroid excretion is striking and reinforces the concept, previously suggested, that the two have a common cellular origin.[13] Nevertheless, the problem of differentiating the two still remains. It is unfortunate in the present case that more urinary steroid analyses could not have been completed during the period of cortisone administration and before operation.

Conclusions

A case of a masculinovoblastoma has been presented.

The values for 17-ketosteroid and "pregnanediol complex" excretion in the urine have been recorded.

Furthermore, the increasing evidence indicting the masculinovoblastoma as an adrenal-cortical type of tumor in the ovary has been cited.

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ENDOMETRIOSIS OF THE PERINEUM

Review of the Literature and Case Report

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THE literature contains a considerable number of reports of endometriosis externa occurring in a variety of sites. Its occurrence in such sites as the Fallopian tube and ovary is somewhat easier to understand than its occurrence in such sites as the kidney,[1] umbilicus,[2] skin of the thigh,[3] vulva,[4] and the perineum. A review of the literature disclosed only 25 cases of endometriosis of the perineum, all developing in specific areas of the perineum that had undergone trauma, obstetrical and/ or surgical.

Review of the Literature

In 1923 Schickele[5] reported the first case of perineal endometriosis. Thereafter, twenty-four cases were reported, three cases by Weis[6, 7] and one case each by different authors.[8-28]

There were a few cases that were incomplete in regard to one or more of the following features: age of the patient, previous obstetrical and surgical history, the interval between the last incident of perineal trauma and the appearance of symptoms, and the follow-up period after excision of the perineal endometrioma.

The reported ages ranged from 23[23] to 45 years.[17] The average age was approximately 38 years. There were approximately 20 patients whose previous perineal trauma consisted of episiotomy or laceration associated with parturition. These 20 cases include 3[8, 19, 27] that were mentioned only briefly during the course of a lecture or conference. Although in each of the 3 cases it was not stated definitely that the "perineal rupture" was associated with parturition, the nature of the discussion and the phraseology suggested that such was the situation. There were 5 parous patients whose symptoms developed subsequent to gynecological surgery. Three patients[5, 17, 21] developed symptoms subsequent to dilatation and evacuation or curettage of the uterus, and 2[11, 16] developed symptoms subsequent to uterine curettage and colporrhaphy.

There were 7 patients[10, 12, 13, 14, 17, 18, 23] who noted the onset of symptoms within six months of the last incident of perineal trauma. There were 13 patients who noted the onset of symptoms twelve months or more after the last incident of perineal trauma. Seven of these patients[6, 7, 20, 21, 26, 28] were asymptomatic for three years or more after perineal trauma. Violet[28] reported the case of a patient who was supposedly asymptomatic for fourteen years after a perineal laceration associated with parturition.

There were 4 cases[5, 11, 14, 21] of recurrence of perineal endometriosis subsequent to excision. All 4 of these patients were treated medically. The most recently reported case of perineal endometriosis was that of Macafee[14] whose patient developed a recurrence within a few months of excision and improved on methyl testosterone. Three patients[7, 23, 26] who were followed for more than

eighteen months developed no recurrences. Nine reports contained no mention of follow-up examinations or were published within twelve months of excision of the endometrioma.

Mrs. F. B., a 25-year-old white gravida ii, para ii, was delivered of two full-term babies in 1950 and 1952, each by means of low forceps accompanied by right mediolateral episiotomy. The postpartum course was uneventful, and the patient was discharged from the hospital in good condition after each delivery. Postnatal office examinations showed no abnormality.

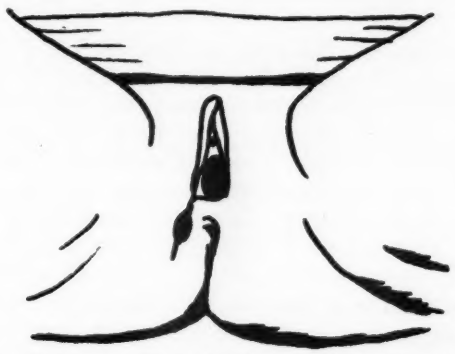

Fig. 1.—Drawing of the perineum of the patient in the lithotomy position, prior to excision of the perineal mass.

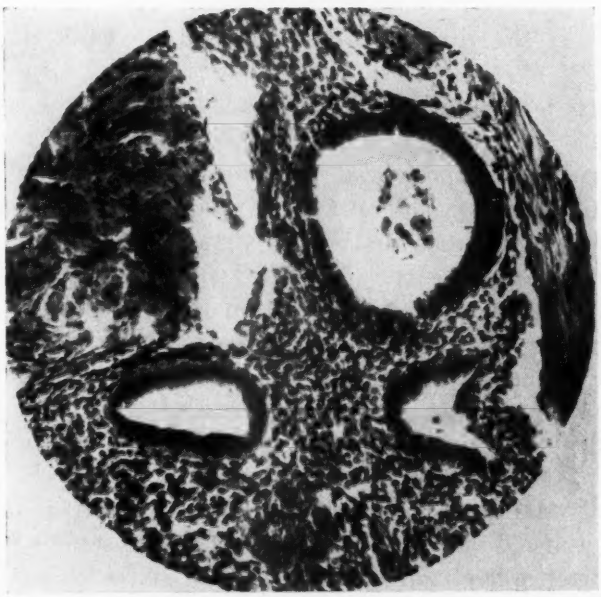

Fig. 2.—High-power photomicrograph of a section through the endometrioma. Three endometrial glands are shown surrounded by endometrial stroma. At the extreme right is subcutaneous connective tissue.

In February of 1953, the patient became aware of a perineal mass the size of a pea. By the following November, the patient observed that the mass increased in size and became painful and tender three days prior to and during menses. After each menstrual period the mass decreased in size and became almost painless. The patient sought gynecologic advice in March of 1954. Pelvic examination at that time disclosed a small mass to the right of the anus, in the scar of a right mediolateral episiotomy. There was no clinical evidence of endometriosis in any other pelvic site.

Perineal symptoms persisted and the patient consented to surgical excision in July of 1954. The old episiotomy scar was reopened and a nodule measuring approximately 3 cm. through its greatest diameter was found buried in the perineum to the right of the anal canal. The nodule and a small portion of external anal sphincter were excised. The episiotomy was repaired and the patient was discharged on the eighth postoperative day in good condition.

The specimen consisted of an irregularly rounded mass of tissue measuring 2 by 2.5 by 1.5 cm., a portion of which appeared cystic. The inner surface was irregular in contour. The remainder of the specimen contained an indurated, hemorrhagic, yellowish-white tissue.

Microscopic examination of the surgical specimen showed areas of endometrial stroma with rounded, somewhat dilated glands noted in most of the areas.*

After discharge from the hospital the patient felt well and menstruated regularly without discomfort until January of 1955, when once again she became aware of the same cyclic perineal symptoms that had prompted gynecologic examination and operation previously. Gynecologic examination in February of 1955 suggested the presence of another endometrioma located in approximately the same site as the previously excised endometrioma. The patient was treated with methyl testosterone, 10 mg. daily for one week prior to the onset of the menstrual period, and almost complete relief of symptoms was reported. After two months of this therapy, testosterone was discontinued and the patient remained practically asymptomatic for another two months. During the past few few months the patient has again become aware of cyclic perineal symptoms.

Summary

1. A review of the literature has disclosed 25 cases of perineal endometriosis.

2. The reported ages ranged from 23 to 45 years; the average age was approximately 38.

3. All patients had experienced previous perineal trauma. There were approximately 20 patients whose previous perineal trauma had consisted of episiotomy or laceration associated with parturition. There were 5 parous patients whose perineal symptoms developed subsequent to uterine curettage and colporrhaphy or dilatation and evacuation of the uterus.

4. Seven patients noted the onset of symptoms within six months of the last incident of perineal trauma; 13 patients noted their symptoms twelve months or more after the last incident of perineal trauma.

5. Four patients demonstrated recurrences subsequent to excision of the endometriomas.

6. The twenty-sixth case of perineal endometriosis is reported. This occurred in a 25-year-old woman, ten months after her second vaginal delivery. There was a recurrence five months after excision of the endometrioma.

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ATRIAL PAROXYSMAL TACHYCARDIA IN PREGNANCY

Case Report of Instance During Labor

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WHILE to the cardiologist paroxysmal atrial tachycardia presents an oft-encountered problem, the likelihood of this acute cardiac disturbance being met by the obstetrician is much more remote. This condition offers an emergency challenge as to selection of the most appropriate drug, while evaluation of such therapy unquestionably can be quite fallacious because of the natural tendency of the dysrhythmia to revert spontaneously to a normal sinus mechanism. Under the circumstance of its occurrence during labor, atrial tachycardia can constitute a disturbing medical emergency and merits definitive, prompt, and predetermined management. Conventional approaches to the problem then are awkward, unreliable, and needlessly time consuming.

For these reasons, an automatic, incisive approach to the control of the tachycardia is most logical.

This 23-year-old white primigravid patient was admitted on Jan. 13, 1954, at 10:50 A.M., in active labor with a normal intrauterine pregnancy. At 1:45 P.M., she developed abrupt, rapid, regular heart action which, despite usual vagal stimulatory measures, persisted. The patient became quite apprehensive and pseudodyspneic, and complained bitterly of palpitation. Because of that, and because of the persistent paroxysmal rapid heart action, cardiac consultation was requested. There were no obstetrical complications. The examination indicated widely spaced similar episodes of sporadic rapid heart rate, beginning abruptly, lasting only for minutes, and either receding spontaneously or relieved promptly by simple methods of vagal stimulation.

While the patient would experience anxiety and tremulousness with these, no more significant features ever presented.

No history of impairment of cardiac functional capacity nor evidence of organic heart disease had been demonstrated. An equivocal history of scarlet fever in childhood was offered.

Because of: (1) active labor, (2) undue persistence of paroxysmal tachycardia, (3) electrocardiographic demonstration of its atrial origin, (4) undesirable psychic reaction to the cardiac disturbance, and (5) failure of the usual techniques to dispel the tachycardia, immediate parenteral digitalization was decided upon. No previous digitalis, procaine amide (Pronestyl) or quinidine had been administered.

Cedilanid (0.8 mg.) was injected rapidly intravenously, and 0.4 mg. was given intramuscularly two hours later.

A normal, live, 6 pound, 8 ounce baby girl was born the next morning without event.

Thereafter, oral digitoxin (0.2 mg.) was prescribed and digitalization was maintained for five days with complete withdrawal then.

There has been no recurrence of paroxysmal atrial tachycardia since.

The subject is discussed and this case reviewed because of the rather unusual time of occurrence of a common disturbance of the cardiac pacemaker. The purpose also is to delineate clearly an appropriate plan of action (particularly drug) to pursue in the event of any occurrence of paroxysmal atrial tachycardia during the period of labor.

General Principles of Treatment of Disturbance of Heart Rhythm

Inevitably, the treatment of cardiac arrhythmias creates confusion when the need for specific therapy arises. This stems largely from the fact that the literature is not only overwhelming in quantity but unorganized in presentation. Basically, one should think of the problem of heart arrhythmias in terms of two fundamental items concerning the organ, itself: (1) Is the heart normal? (2) Is there heart disease?

When one is dealing with rhythmic disturbances of the *diseased* heart, two further basic questions arise. These are: (1) Is it the mere presence of the arrhythmia itself which is potentially lethal? (2) Or is the rapid ventricular rate associated with the abnormal rhythm the important factor which may contribute to increased morbidity or even death of the individual? Obviously, some prior knowledge of the nature of the arrhythmias is necessary in order to make these judgments, but if this is understood, then the problem of treatment is clear and simple.

Choice of Drug.—To dispose of the second problem first, if it is the rapid ventricular rate, alone, which constitutes the threat to life, one actually has no choice of therapeutic agent! I say this because there is only *one* cardiac drug (actually, group of drugs) which will decrease the ventricular rate consistently, dependably, and invariably. That drug is digitalis.

At once we see that the problem of cardiac arrhythmias has been narrowed down to the group in which the arrhythmia, itself, inherently possesses fatal possibilities. Predominantly, these arrhythmias are ventricular in origin, i.e., multifocal premature contractions, ventricular tachycardia, ventricular fibrillation, etc. (The remaining disturbances of rhythm essentially are concerned with atrioventricular or intraventricular conduction and are not, technically, rhythmic disturbances, but rather abnormalities of impulse propagation.)

Almost all ventricular arrhythmias can be treated with one of two drugs, (1) Pronestyl (procaine amide), (2) quinidine. Pronestyl usually is the drug of choice, and most certainly is if there is an intraventricular conduction defect, although Pronestyl likewise can cause such a change. Procaine amide has the marked disadvantage of being a potent hypotensive drug and must be given parenterally extremely cautiously. Quinidine, to be effective, requires doses so large as to induce often the rather undesirable side effects of marked nausea, vomiting, flushing, etc. Either drug should be used parenterally *only* with continuous electrocardiographic control, particular attention being paid to their extreme propensity for causing delayed stimulus transmission. The marked hypotensive effect of Pronestyl can be combated reasonably successfully with pressor agents of the Levophed or Vasoxyl type.

Specific Treatment of Atrial Paroxysmal Tachycardia.—Paroxysmal atrial tachycardia may be diagnosed reasonably precisely at the bedside if the patient develops a sudden, rapid, regular increase in heart rate with a frequency in range of 160 to 260 per minute and if the attack is characterized by an abrupt onset with either abrupt recession or no change. Bedside techniques designed to dispel the tachycardia include a number of maneuvers which range from "the laying on of hands" to specific techniques designed to stimulate the vagus nerve. Sometimes the electrocardiographic technician will not be able to obtain a tracing before the rapid rhythm disappears spontaneously. This seems most likely to happen in cases which are diagnostically most problematic!

Without being too facetious, may I indicate that a number of the so-called bedside maneuvers give the patient the impression that the doctor is either conducting an experiment in clinical physiology or has become so confused by the urgency of the situation requiring solution that he performs a number of "mystic" maneuvers to take away the evil spirits! All of which is to say that the methods of interrupting paroxysmal atrial tachycardia, other than drug therapy (and indeed, including some of this) are just as likely as not to be ineffective.

NORMAL SINUS RHYTHM

Fig. 1.—Normal sinus rhythm. The graphic features of importance here include particularly the normal rate and the very normal appearance of the P waves (the smoothly rounded wave immediately preceding the thin-lined, triangular QRS complex, indicating ventricular depolarization), indicative of atrial contractile activity.

Conventional Diagnostic-Therapeutic Maneuvers.—Gentle massage of the carotid sinus area requires a certain bit of dexterity and is by no means predictably remedial. It is not without danger, since certain individuals may manifest angiocerebral syncope upon carotid sinus stimulation. Particularly in elderly age groups, and certainly with patients having questionable or unrecognized temporal arterial vascular disease (i.e., temporal arteritis), this procedure can be more than a little dangerous.

Eyeball pressure, in order to be effective, must produce retrobulbar pain and this is not especially comforting to the recipient. Further, few individuals take delight in having vomiting induced for the purpose of reacquiring a normal sinus rhythm following an attack of paroxysmal atrial tachycardia. The disturbance, itself, is most often accompanied with little subjective distress in the first place.

Electrocardiographic Diagnosis.—Electrocardiographic recognition of paroxysmal atrial tachycardia is relatively easy if the tracing presents: (1) regularity of rhythm; (2) segmental equality of amplitude of all complexes; (3) regular alternating sequence of atrial, followed by ventricular, depolarization inscriptions. The rate varies from 160 to 260 per minute. Clinical history is valuable if the story of an abrupt onset is obtained.

Otherwise, the spontaneous conclusion of the tachycardia or its disruption by the bedside technique described is a helpful guide in interpreting the meaning of the tracing. In some instances P waves are singularly lacking, even in the leads, for example, Lead II, where ordinarily they are identifiable readily. Perhaps a special lead V_{3R} may be recorded, to allow for absolute identification of the atrial activity. If P waves still are not delineable, the momentary diagnosis can be considered to be a "supraventricular" tachycardia, which will allow the same appropriate treatment in the absence of a finer diagnosis. Perhaps a previous "control" electrocardiogram on the same patient might be available for study; or, a subsequent electrocardiogram may be obtained in an attempt to evaluate the meaning of the paroxysmal tachycardia. In any event, whether the supraventricular tachycardia occurring paroxysmally is labeled as such, or under the more specific heading of paroxysmal atrial tachycardia, the treatment essentially is unchanged. Similar diagnosis and management may be used in the case of nodal tachycardia where the rate tends to be somewhat slower and simulates a very rapid sinus tachycardia, except for the acuity of onset. Here, again, is demonstrated the value of some historical information.

PAROXYSMAL ATRIAL TACHYCARDIA

Fig. 2.—Paroxysmal atrial tachycardia. For convenience to the obstetrician, the drawing is idealized, indicating particularly the appreciable increase in total cardiac rate and the present, but somewhat deformed, P waves.

This schematic presentation does not hold true in the majority of instances of paroxysmal atrial tachycardia, for often the P waves are quite aberrant, or even indiscernible except by the use of special electrocardiographic techniques (if then!).

See text for concise amplified discussion of the electrocardiographic recognition of paroxysmal atrial tachycardia, often referred to simply as "P.A.T."

Digitalis Glycoside Mandatory.—Drug therapy is the most effective, direct, and predictable manner of treating efficiently the patient who has experienced an episode of paroxysmal atrial tachycardia, but this drug therapy must be limited to a quick-acting glycoside preparation of Digitalis or Strophanthus.

All other pharmacologic agents have far more serious disadvantages than have digitalis or digitaloid preparations.

Disadvantages of Non-digitalis Drugs.—In my opinion, the pharmacologic demonstration of effective action upon the vagus nerve remains properly the province of the physiology or pharmacology laboratory. Other than this, drugs have the following drawbacks to consistent clinical effective use:

1. They may be dangerous (e.g., Mecholyl).
2. Their actions may be unpredictable.
3. Their effect may be unpleasant to experience (e.g., emetics).
4. The measures are scarcely more than 50 per cent, if that much, effective regularly.
5. They may be contraindicated in the presence of hypertension and/or coronary artery disease, in which case some other method must be resorted to anyway.

6. They may have side effects (e.g., quinidine) which are more disturbing to the patient than the paroxysmal episode.

7. They may be allergenic or actually hematotoxic.

Both bedside maneuvers and pharmacologic procedures other than digitalis should be considered as "trial-and-error" types of specific therapy which are both cumbersome and indirect, as well as primitive.

Reason for Failure of Digitalis.—If, as is most often the case, the etiology of paroxysmal atrial tachycardia cannot be demonstrated, then the immediate drug of choice is parenteral digitalis glycoside, provided the episodes require treatment at all. Four major exceptions to the predictable effectiveness of this drug in the presence of paroxysmal atrial tachycardia are cases of: (1) acute myocardial infarction, (2) hyperthyroidism, (3) toxic myocardosis, or, (4) infectious myocarditis.

How to Use the Digitalis.—Especially if no history of previous medication is obtainable, the initial dose of digitalis glycoside (e.g., Cedilanid) should be half the normal average digitalizing dose, i.e., 0.8 mg., given rapidly intravenously. Subsequently, the remaining half-digitalization dose may be given in two increments, each about two hours apart. Variations upon this dosage, of course, will occur in any specific individual instance.

Digitalization may be maintained with an immediate dose of long-acting digitalis, such as digitoxin, 0.2 mg. for three to five days, at the end of which time a decision can be made as to the advisability of: (1) simply discontinuing the digitalis, (2) maintaining digitalization, or (3) discontinuing digitalis and advising sporadic dissipating quinidine for isolated episodes.

Which of these alternatives is chosen depends largely on etiological diagnosis and detailed history of the paroxysms.

Summary

1. An instance of paroxysmal atrial tachycardia in labor, an unusual cardiac emergency during pregnancy, is presented.

2. General principles of the treatment of disturbances of heart rhythm during labor are outlined.

3. Drug therapy, particularly for paroxysmal atrial tachycardia, is summarized for the obstetrician who may rarely encounter such an uncommon experience.

4. Use of a digitalis glycoside as the mainstay of definitive emergency treatment is emphasized.

To Dr. Newlin F. Paxson, Chief of the Division of Women and Head of the Department of Obstetrics; to Dr. Harry D. Evans, Jr., Associate Professor of Obstetrics; and to the late Dr. Henry L. Crowther, may I express my appreciation for their cooperation in facilitating improved patient care through the medium of coordinated obstetric-cardiologic therapy.

I also wish to express my appreciation to Dr. Lowell L. Lane, Professor of Clinical Medicine, Hahnemann Medical College, for his wisdom and helpfulness in guiding younger aspirants in the field of the heart in pregnancy.

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PROLAPSE OF THE UTERUS ASSOCIATED WITH PREGNANCY

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THE earliest reference to a gravid prolapsed uterus is found in *The Anatomical Exercitations* by William Harvey, 1653[1]: "And now at this time, it [the prolapsed uterus] was large and dangling between her leggs. It grew at best bigger than a man's head, being then a hard tumor, and hanging down to her knees did much pain her, so that she could not goe, but upon all foure. I did suspect it to be a cancer of the Wombe, and therefore did bethink my selfe of ligature and cutting it off: but the following night an infant perfectly shaped of a span long was cast of that tumor, but it was dead."

In the year 1773, a case report of a complete uterine prolapse and pregnancy was given in the *Journal de Médecine et Chirurgie.*[1] Guillemot, quoted by Montgomery, collected 9 cases of pregnancy and prolapse in 1863.[1]

Keettel[2] in 1941 reported 3 cases of prolapse of the uterus complicating pregnancy and analyzed these along with 167 cases collected from the literature.

Incidence of Prolapse of the Uterus With Pregnancy

Prolapse of the uterus associated with pregnancy is a rare complication. Keettel had one case in 13,000 deliveries in a period of over 14 years. From another hospital he reported one case which occurred in 2,000 deliveries over a period of 10 years. Kibel[4] in the Bronx Hospital reported one case in 15,696 deliveries over a period extending from Jan. 1, 1938, to Nov. 1, 1943. This present report includes 4 cases which occurred among 16,542 obstetric admissions at the University Hospitals between July, 1940, and January, 1956.

Case Reports

CASE 1.—G. N. (Hosp. No. 45-7260), a 47-year-old, married, white secundipara was admitted on May 3, 1955. The exact date of her last menstrual period was not known; however, the estimated delivery date was May 2, 1955.

On admission, the fundus of the uterus was 2 fingerbreadths below the xiphoid, and a near-term fetus was presenting transversely. Her blood pressure was 148/80 and there was slight edema of the lower extremities. The laboratory tests were normal. The cervix protruded 6 cm. beyond the introitus and was markedly edematous with several large areas of ulceration around the external os (Fig. 1).

Course in the Hospital.—The patient was placed on bed rest and continuous saline dressings were applied to the cervix. The edema rapidly disappeared and the ulcerations rapidly improved. Within a few days it was possible to replace manually the prolapsed cervix which was maintained in place by a pessary. The cervix remained in the vagina and the local ulcerations healed. Although four days after admission the membranes ruptured spontaneously, an external version could be done, converting the transverse presentation to a vertex. It was decided not to stimulate labor because of the small size of the baby. The patient was given

prophylactic antibiotic therapy. Uterine contractions started on May 13; the first stage lasted 6 hours, the second 24 minutes, and the third 3 minutes. No lacerations occurred and no episiotomy was necessary. The blood loss was estimated at 125 c.c. The baby was cyanotic and flaccid at birth, but responded well to oxygen therapy. Its weight was 2,500 grams. It did poorly, however, and died 4 days later.

The patient had an afebrile and uncomplicated puerperium and was discharged on May 19. The cervix was well healed but was elongated and hypertrophied and there were a moderate rectocele and cystocele. The patient was advised to return in two months for plastic repair. On Aug. 11, 1955, a vaginal hysterectomy with an anterior and posterior vaginal wall repair was done. The postoperative course was uneventful.

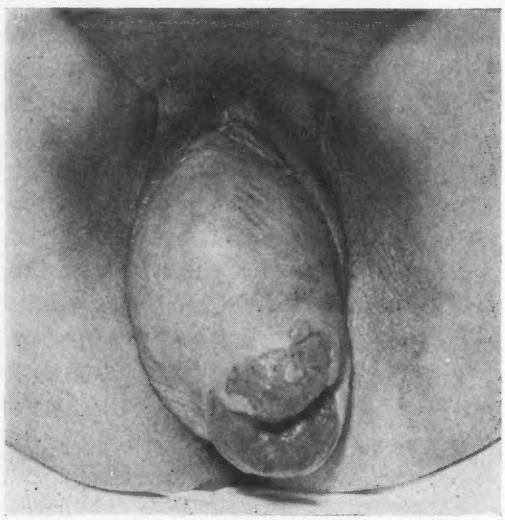

Fig. 1.

CASE 2.—S. R. (Hosp. No. 41-6216) was a 23-year-old white woman, gravida iii, para ii. In her second pregnancy, 2 weeks before delivery, she had developed a prolapse of the uterus, with a protrusion of the cervix beyond the introitus. The delivery was normal and the cervix returned to its normal position. During the present pregnancy, she had an uneventful prenatal course until the thirty-second week when she noted the cervix protruding beyond the introitus; this was at first relieved by bed rest and elevation of the hips.

The admission examination was negative except for the pelvic findings. The cervix uteri was prolapsed beyond the introitus 3 cm. and was badly eroded and edematous. The patient was placed on bed rest in the Trendelenburg position and glycerin Mercurochrome packs were applied. After 12 hours the cervix was completely reduced and did not appear again. Elective induction of labor with rupture of the membranes was done and the patient was delivered spontaneously after a total labor of 1 hour and 34 minutes. The infant was normal and weighed 3,620 grams.

The puerperium was afebrile. At the time of discharge, a pelvic examination disclosed a large cystocele and partial prolapse of the cervix. She returned in 6 months for plastic repair at which time a Watkins interposition operation with anterior and posterior vaginal wall repair and tubal ligation were performed.

CASE 3.—S. C. (Hosp. No. 40-16043) was a 31-year-old white woman, para iv, gravida v, who was admitted to University Hospitals at the thirty-sixth week of pregnancy with the complaint of prolapse of the cervix which had occurred 24 hours before. When she was admitted, the cervix was protruding 3 cm. beyond the introitus and was ulcerated. It bled

easily upon sponging. The patient went into labor that same day and was delivered without complications of a normal full-term infant. The puerperium was uneventful and the patient was asked to return for a plastic repair. Six months later a Fothergill operation was performed.

CASE 4.—M. G. (Hosp. No. 51-6009), a gravida ix, para viii, was admitted at 32 weeks because of stress incontinence and prolapse of the cervix beyond the introitus. Physical examination was essentially normal. The cervix was protruding beyond the introitus. The patient was given no treatment except bed rest. She went into labor spontaneously and delivered a full-term infant weighing 3,580 grams. The puerperium was uncomplicated. She was advised to have a plastic repair in three months but did not return.

Literature

Of the 170 cases prior to 1941, only 140 had adequate case records. Of the 170 patients 19 were primigravidas, 82 were multigravidas, and 69 were not identified. During the course of pregnancy, 15 per cent had early abortion. Normal delivery occurred in 45.7 per cent. Dührssen's incisions of the cervix followed by forceps accomplished delivery in 27.1 per cent while in 29.3 per cent Dührssen's incisions alone permitted spontaneous birth. Version and extraction was performed in 4.3 per cent and craniotomy in 7.8 per cent. A cesarean hysterectomy was required in one case. The fetal death rate was 22.1 per cent and the maternal death rate was 6.3 per cent, nearly all the deaths being due to sepsis. It should be noted that most of the patients who died were delivered prior to the discovery of chemotherapeutic and antibiotic agents.

Complications of Pregnancy.—In 12 out of 22 cases collected since Keettel's publication in 1941, the prolapse started during pregnancy, while in 10 it occurred in a previous pregnancy or after a previous delivery. Of these 22 cases (Table I), 16, or 72.7 per cent, were vertex presentations. In 3 the presentation was not indicated. One patient had twins.[8] One case reported by Kibel was a breech presentation with prolapse of the cord and death of the fetus. Three of the 4 cases from the State University of Iowa Hospitals were vertex presentations; one was a transverse lie. There were 3 premature infants, or 13.6 per cent. There were one stillbirth and one neonatal death. The perinatal mortality was 9 per cent. There were no maternal deaths reported.

TABLE I. SUMMARY OF 22 CASES OF UTERINE PROLAPSE WITH PREGNANCY

SOURCE	YEAR PUBLISHED	NO. OF CASES	PARITY	DELIVERY PROCEDURES
Mitra, Nandi[3]	1943	1	Multipara	Spontaneous
Kibel[4]	1944	1	Multipara	Spontaneous—infant stillborn
Patterson[5]	1944	1	Multipara	Spontaneous—infant premature
Rosenfeld[6]	1948	2	Secundipara	Cesarean section
Klawans, Kanter[7]	1949	4	3 primiparas, 1 secundipara	Spontaneous
Hawkins[8]	1949	1	Multipara	Spontaneous
Israel, Weber[9]	1950	5	3 secundiparas, 2 multiparas	3 spontaneous, 1 forceps, 1 version
Yellen, McNeill[10]	1954	2	Multiparas, 1 with repeated abortions	1 spontaneous, 1 Dührssen's incision
London, Peck, Fond[11]	1954	1	Secundipara	Spontaneous
Mufarrij (this report)	1956	4	2 secundiparas, 2 multiparas	3 spontaneous, 1 external version

Labor started spontaneously at term in 16 out of the 22 cases, or in 72.7 per cent. In one case no information could be obtained about the type of labor. Labor was induced in 3 patients at term and in 2 there was spontaneous premature rupture of the membranes.

Types of Delivery.—Thirteen out of 22, or 59 per cent, had normal deliveries. Only one patient, or 4.5 per cent, was delivered after Dührssen's incisions were made.[10] Israel and Weber[9] delivered one patient by a bimanual podalic version and another with low forceps. They had bilateral lacerations of the cervix in one case. Kibel's case was a breech which was complicated by prolapse of both the uterus and the cord, and resulted in a stillborn baby. Rosenfeld[6] delivered both of his patients by cesarean section after a failure of a test of labor. One of the 2 had twins. Klawans and Kanter[7] reported one case with puerperal hemorrhage.

In one case, or 4.5 per cent, there was a history of repeated abortions prior to the present pregnancy which ended successfully.

The puerperium was normal in all cases; there were no morbidity or other complications.

The treatment of prolapse during pregnancy varied with the different authors. Bed rest and/or a pessary was used in about 40.9 per cent of the cases. Vaginal packs and perineal pads were used by different authors. One patient did not have any treatment and in another one the treatment was unknown.

Comment

It is interesting to observe how much discussion in the literature concerns whether the prolapse was complete or not and whether it was true prolapse or only elongation of the cervix. According to the descriptions given by the different authors, there is no doubt that the great majority of cases are true prolapse. It is of instructive value to quote Israel and Weber, who emphasized the situation when they said: "From the standpoint of obstetrical management, it is only of academic interest whether the prolapse antedated the pregnancy or developed after its onset; whether it is really uterine prolapse or merely an elongation of the cervix; or whether the prolapse persists after the postpartum period or corrects itself, for if the cervix presents itself at the vulva, the obstetric problem remains the same."

The incidence of abortion in 22 cases was 4.5 per cent, as compared with 15 per cent as reported by Keettel in a previous publication. Fetal death was quite low and no maternal deaths were reported. One may attribute this improvement to the advent and use of antibiotics, and to the conservative treatment followed by the different authors. Pessary and/or bed rest may be a good treatment for the prolapsed cervix which will often dilate without difficulty to allow spontaneous delivery.

Summary

Four cases of prolapse of the uterus associated with pregnancy are presented. These occurred among 16,542 obstetrical admissions at the University Hospitals, Iowa City, Iowa, between July, 1940, and January, 1956.

Eighteen other cases occurring in the same years were collected from the literature.

In recent years, there has been a shift toward conservative treatment. Pessaries, bed rest, vaginal packs, and perineal pads were the treatments of choice.

The frequency of abortion was much less than previously reported.

There were no maternal deaths reported. The fetal death rate was quite low. The puerperium was normal in all cases; there was no puerperal morbidity or other complications. One may attribute this improvement to the advent and use of antibiotics and the conservative treatment used by different authors.

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SICKLE-CELL CRISIS IN PREGNANCY NEAR TERM

Report of a Case

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During the past four years, articles in current literature have made many contributions pertaining to sickle-cell anemia associated with pregnancy. Obstetricians have reviewed these articles with great interest. In a study made of this literature Anderson and Busby[1] reported 33 cases and added 11 cases, with a total maternal mortality of 15.9 per cent and fetal loss of 33.3 per cent through abortions and death of viable infants. Fouché and Switzer[5] reported 29 cases with 9 maternal deaths. Beecham and Beecham[2] added a total of 37 cases with 4 maternal deaths, giving a combined total of 66 cases with 13 maternal deaths, or a maternal mortality of 20 per cent in this series.

The question arises why more articles have not been written about sickle-cell anemia. Caruso[4] gave a possible answer when he suggested that the relative paucity of cases can be attributed to the fact that most patients with sickle-cell disease die early in life and that there is also the possibility of infertility with this blood dyscrasia. Fouché and Switzer also stated that they were able to find only 23 cases of actual sickle-cell crisis during pregnancy reported in the literature.

The present case is presented because it points out the problems encountered in the pregnant woman who is near term when the manifestations of sickle-cell crisis become obvious. The present case is further complicated by a severe pre-eclampsia and a past history of rheumatic heart disease.

Case Report

A 16-year-old primigravid Negro woman was admitted to the obstetrical service of Mt. Carmel Hospital on Sept. 9, 1955. Her expected date of confinement was Sept. 23, 1955. Routine prenatal examination had revealed a weight gain of 14 pounds in the 15 days prior to admission, with an elevation of blood pressure from 120/76 to 160/90 during this same period. Also noted was the fact that the hemoglobin had dropped from 60 to 40 per cent. She was admitted because of these findings and for further evaluation.

On admission, the patient stated that she had noted ankle swelling, weakness, and dyspnea for the two weeks prior to admission. She had noted slight dizziness for the two days prior to admission with generalized aching.

Her past history was remarkable in that the patient was said to have had acute rheumatic fever at the age of 3, characterized by swelling of the joints, low-grade fever, and residual heart murmurs. Furthermore, she stated that she had had several exacerbations of the heart disease characterized by ankle edema and dyspnea. Following one exacerbation at the age of 12 she was placed on bed rest for six months. During her pregnancy, the patient had received 0.2 mg. of digitoxin daily and had been placed on a low-sodium diet. There was no familial history of hemolytic disease.

Examination showed a well-nourished Negro girl in no marked distress. The blood pressure was 160/98; pulse, 104; weight, 146 pounds; temperature, 98.6° F. The mucous membranes were quite pale. The patient was mildly orthopnic. The heart was enlarged to the anterior axillary line. There was a systolic thrill located to the left of the sternum in the third intercostal space. A Grade III low-pitched systolic murmur was heard over the entire precordium but best at the aortic and mitral areas. Râles were heard in both lung bases posteriorly. The uterus was enlarged to approximately the size of a 9 months' pregnancy. Fetal heart tones were present in the left lower quadrant and were normal. The spleen and liver were not palpable. There was 4 plus pitting edema of both ankles.

Admission laboratory studies were as follows: urine, specific gravity 1.008; sugar was negative and the microscopic examination was not remarkable. There was 600 mg. of albumin present. The erythrocyte count was 1.8 million; the leukocyte count 12,090; hemoglobin 30 per cent (4.5 Gm.); the differential count was myelocytes 2, juvenile forms 3, stab cells 10; segmented cells 76; lymphocytes 9. The hematocrit was 15 per cent. There were 272 erythroblasts per 100 white blood cells. The uric acid was 4.9; blood urea nitrogen, 15.3; icterus index, 8.1; van den Bergh test, direct, negative; indirect 0.93; Coombs test, negative (direct and indirect). A sickle-cell preparation was reported as positive. Erythrocyte fragility was decreased. The coagulation time was 4.5 minutes; bleeding time, 1.25 minutes; platelets, 81,600. A chest x-ray revealed considerable generalized enlargement of the heart without evidence of congestion. Electrocardiogram showed flattening of the T waves which could be interpreted only as nonspecific myocardial damage, but was otherwise normal.

The patient was placed on strict bed rest with sedation by phenobarbital and an intensive antitoxemia regime was started at once. Combination diuretic therapy was used with the patient receiving 4 Gm. of ammonium chloride 4 times daily for 3 days and then Diamox, 250 mg. daily. Mercuhydrin, 2 c.c., was given on two occasions intramuscularly. Magnesium sulfate, 4 c.c. in each hip, was given every six hours. The patient had previously been on digitoxin, 0.2 mg. daily, and this dosage was regulated during the first two hospital days for maximum effect.

On the evening of the first hospital day blood replacement was begun by giving 200 c.c. of packed erythrocytes slowly. This was repeated on the second, third, and fourth hospital days with a total of 800 c.c. given. Packed erythrocytes were used in order to reduce the amount of sodium as well as the total volume of fluid necessary to improve the circulating hemoglobin level. On this regime the patient lost 13 pounds by the fifth hospital day. Pitting edema was absent. The blood pressure was maintained around 130/90, and the urine became free of albumin. The chest was clear and there was no dyspnea or orthopnea. The hemoglobin rose to 9.6 Gm. with a red blood count of 2.99 million and a hematocrit of 33 per cent.

The patient began to have irregular contractions on the fifth hospital day. The membranes ruptured spontaneously and active labor began. During labor no scopolamine was used and a broad-spectrum antibiotic was given regularly. Saddle block anesthesia was planned but because of the rapidity of labor was not accomplished. Seven hours and 40 minutes after the onset of labor the patient was delivered under light ether-oxygen anesthesia of a 5 pound, 6 ounce living female infant. One-half hour following delivery the patient was given 300 c.c. of whole blood as replacement.

The postpartum course was unremarkable. She was placed on a broad-spectrum antibiotic and watched closely for signs of infection. The hemoglobin remained around 9.5 grams. She was discharged on the third postpartum day.

The patient returned to the hospital on the ninth postpartum day for follow-up evaluation. Physical examination was unremarkable except for the persisting Grade III low-pitched systolic murmur heard best at the aortic and mitral areas. Chest x-ray revealed borderline enlargement of the left ventricle. Skull films for osseous changes of sickle-cell disease were negative. A sickle-cell preparation was again reported as positive.

The van den Bergh test was negative in the direct test; and was 0.71 in the indirect test. The erythrocyte count was 3.11 million; hemoglobin 58 per cent (9 Gm.); hematocrit 30 per cent. The patient appeared well and had no subjective complaints.

Summary

A case of sickle-cell crisis occurring near term pregnancy has been presented. This case was further complicated by the development of severe preeclampsia which has been shown in the literature to be more prone to develop in the patient with sickle-cell disease.

The main problem presented is that of replacing hemoglobin to a blood volume greater than would be found in the nonpregnant state. The fluid retention of toxemia added to the difficulty of this problem. For these reasons the patient was treated rigorously to accomplish diuresis while hemoglobin was being replaced very slowly with packed erythrocytes. The object of treatment was to raise the hemoglobin level to a point safe for delivery without overloading the cardiovascular system or precipitating further difficulties with the sickle-cell disease.

The heart murmurs heard in this case are difficult to explain on other than a rheumatic or congenital basis. It is a fact that the patient with sickle-cell disease in crisis may have joint swelling, low-grade fever, and heart murmurs indistinguishable from those of rheumatic fever; however, the persistence of these murmurs between episodes of crisis would not be likely to occur. Burke and Rosenfeld[3] reported a similar case in 1953 in which the diagnosis of rheumatic heart disease had been made prior to the time sickle-cell disease was proved. In this case, however, the murmurs did not persist between episodes of crisis, and it was justly assumed that the original diagnosis was in error.

The over-all plan of therapy in this case follows that suggested in the literature. This includes replacement of blood, use of antibiotics to prevent infection, reduction of the amount of trauma associated with actual delivery, and rigorous treatment of complicating factors such as toxemia. Caruso suggested that since the sickle cell is a poor oxygen carrier, continuous oxygen therapy may be advisable during labor.

Postpartum care was directed toward replacement of blood lost during delivery, continuation of antibiotic therapy, and general supportive care.

From this case presentation it can be seen that close supervision of the prenatal course of all pregnant Negro patients with early efforts to diagnose the presence of sickle-cell disease will facilitate early treatment and safe delivery.

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INTERLOCKING AND COLLISION IN MULTIPLE PREGNANCIES

Two Case Reports

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COLLISION and interlocking of twins are extremely rare complications of multiple pregnancy. In spite of their infrequency most textbooks of obstetrics make some reference to them. Most young practitioners when confronted with their first few multiple births will be overly concerned about the possibility of the babies becoming entangled or locked. The incidence of locked twins, as reported by von Braun of Vienna, is once in 90,000 deliveries or approximately once in 1,000 twin births.

There are in general two divisions in which the cases can be classified.[1, 2] Everyone is familiar with the chin-to-chin locking that occurs when the first twin presents by the breech and the second by the vertex. This division has been classified as locked twins while a second group has been called collision of twins. A number of variations can occur with collision. Examples are: (1) two heads trying to enter the pelvis simultaneously (such a case follows), (2) two breeches trying to enter the pelvis simultaneously, (3) the aftercoming head of the first twin in breech presentation being arrested against the trunk of the second twin in a transverse lie. English authors[3, 4] use a broader classification and classify locked twins and collision under one heading of "twin locking."

Collision of Twins

M. H. was a 22-year-old primigravida at term on Aug. 7, 1953. The pregnancy progressed normally and on July 23, 1953, a clinical diagnosis of twins was made. X-ray pelvimetry on July 24 confirmed the diagnosis and showed normal pelvic measurements. One fetal skull was in midpelvis with the spine on the mother's right side. The second fetal skull was in the right upper quadrant with the fetal spine on the mother's left side. The patient went into labor at 1:00 P.M. on August 12. Both infants were in vertex presentation. Labor progressed slowly during the day and a sterile vaginal examination performed at 11:35 P.M. showed the cervix to be completely effaced and 3 cm. dilated. The first fetus presented as a vertex in a right occipitoposterior position and was at a plus 1 station. The membranes were ruptured artificially. Labor progressed slowly and the following morning the cervix was 4 cm. dilated with the head at a plus 2 station. It was evident that the patient had uterine inertia. She was started on antibiotics and was given intravenous dextrose (5 per cent) containing Pitocin at 1:00 P.M., August 13, after 24 hours of an inertial type of labor. The intravenous Pitocin was continued during the remainder of the day with fair results. A sterile vaginal examination at 11:30 P.M. that day showed the cervix to be 7 cm. dilated. The presenting part was at a plus 2 station and was in a right occipitoposterior position in a deflexed attitude. The patient was given morphine for sedation and rested well during the night. The following day she was again started on intravenous Pitocin. That evening she was again taken to the delivery room. The

presenting part, on vaginal examination, was just off the pelvic floor in a right occipitoposterior position with the head slightly deflexed. The cervix was felt about the infant's head and was described by the operator as being 9 cm. dilated. It was the operator's opinion that vaginal delivery would offer greatest safety to both the mother and her infants. The use of Dührssen's incisions followed by low forceps delivery was contemplated. The fetal heart tones remained good. The patient was given a saddle block anesthesia and prepared for delivery. The cervix was easily pushed over the head making Dührssen's incisions unnecessary. Premature forceps were applied, a right mesiolateral episiotomy was performed, and the infant was delivered after three moderately hard tractive efforts. The infant did not make any effort to breathe and resuscitative efforts were unsuccessful. Immediately after the delivery of the first infant, the operator's hand was inserted into the uterine cavity. The second twin was found to be presenting by the vertex. The head was pushed into the pelvis by fundal pressure, and the membranes were ruptured. The infant was delivered spontaneously within minutes and cried immediately.

Examination of the first infant showed that the head, neck, and shoulders were discolored and edematous. The chest was flattened and concave. The lower portion of the infant appeared pale. A depression in the infant's chest fitted almost perfectly a 10 to 12 cm. sphere, the size of a normal fetal head. When such an object was placed in the cavity it was seen that the infant's chin was pushed upward and the edema of its neck, which was mostly lateral, fitted closely around the edge of the object. It was known that during labor the head of the second infant was low and anterior in the midline. It was the impression of the operator that the difficulties of this labor and delivery could best be explained if it were presumed that the head of the second fetus lay over the chest of the first, whose back was lying directly posterior during labor and in the last days of gestation. During labor the infants came down as a unit, thereby producing an unrecognized dystocia. This probably also accounted for the uterine inertia and prolonged labor. The first infant was a small male and weighed 1,900 grams, while the second was also a male, weighing 2,965 grams. Both gross and microscopic examination of the placenta showed that they were double ovum twins. On autopsy there was an incomplete laceration of the tentorium cerebelli with extravasation of blood into the dura but no injury of major vascular channels was seen.

Locking of Triplets

M. L. was a 23-year-old primigravida at term on March 24, 1955. On Jan. 22, 1955, it was suspected that the patient was going to have twins. An x-ray of the abdomen showed the presence of triplets. At 12:30 A.M. the morning of February 4, the membranes ruptured spontaneously. On admission approximately one hour later, a sterile vaginal examination was performed to rule out any possibility of prolapsed cord. The presenting part was floating. The cervix admitted one finger and was 50 per cent effaced. A foot could be felt through the cervical os but no cord was palpated. The patient was placed in bed and observed. On abdominal examination a head could be felt in the right lower quadrant of the abdomen. A second head was found in the left lower quadrant at a slightly higher level, and a third head was located in the right upper quadrant. At approximately 10:00 A.M., the patient went into spontaneous labor with the first baby presenting as a complete breech in a right sacrotransverse position. Seven and one-half hours later the cervix was completely dilated with the breech at a plus 2 station. With pudendal nerve block anesthesia, spontaneous delivery of the breech to the level of the umbilicus was permitted over a left mediolateral episiotomy. Assistance was given for the delivery of the arms and shoulders. The anterior arm was delivered first. The infant's body was elevated and the posterior arm was delivered in the hollow of the sacrum. Some slight difficulty was encountered in performing this maneuver, which gave an impression that the aftercoming head was not readily entering the maternal pelvis. The operator's left hand was inserted posterior to the baby, and it was found that the head of the second infant was entering the pelvis. The second infant was presenting by the face, left mentum anterior. The aftercoming head of the breech baby was locked above the head of the

second infant. The patient was immediately given cyclopropane anesthesia. The head of the second infant was then pushed manually out of the pelvis thereby permitting the aftercoming head of the first infant to enter the pelvis and be delivered. The first infant was markedly asphyxiated but responded to resuscitation. The second infant again presented as a left mentum anterior. It was delivered by means of forceps and was only slightly asphyxiated. The third baby presented as a vertex in a left occipitoanterior position and was delivered spontaneously. The first infant weighed 1,810 grams and was a male. The second infant was also a male and weighed 1,710 grams. The third infant, a female, weighed 1,925 grams. The two male infants were identical as determined by examination of the placenta and later development. All three infants survived and were apparently developing normally when seen and examined a year later.

Comment

Interlocking and collision of twins usually cannot be predicted prior to the onset of labor and are usually not detected until the time of delivery. However, the operator should keep in mind the remote possibility of collision when labor is prolonged or does not pursue a normal course. X-rays of the pelvis should be of aid in making a diagnosis of collision during labor.

The etiology of locking and collision has been ascribed to small babies, large pelvis, or a deficiency of amniotic fluid.[1, 3] Lawrence,[5] in 1949, reviewed 28 cases published since 1907 and found that 23 were in primigravidas and regarded this as a strong predisposing factor. The reason for this is not clearly understood. Of the 28 cases, 15 were chin-to-chin locking. In 9 patients both infants presented by the vertex. A transverse collision occurred in 3, and in one both infants presented by the breech. Lawrence reported an over-all fetal mortality rate of 39 per cent. The first fetus was lost in more than half the entire series. The locking variety apparently was most dangerous to the fetus, with 13 out of 15 being stillborn. There were no maternal deaths in the 28 cases reviewed.

Treatment is variable and depends upon the circumstances found in each individual case. In true chin-to-chin locking, if the pelvis is large and the babies are small, an attempt should be made to dislodge and disengage the heads.[6] This can best be done if locking is recognized prior to the delivery of the arms and shoulders. The operator inserts his hand posterior to the neck of the breech and grasps the head of the second twin. Upward pressure is then applied to both the head of the second twin and the trunk of the first infant. As the head of the second twin is elevated, in favorable cases, it will be felt to slip past the aftercoming head of the breech baby. Gentle downward traction on the breech brings the aftercoming head into the pelvis so that delivery can be executed. It is believed that deep general anesthesia is best for this maneuver; it not only insures a quiet patient, but it relaxes the uterus, permitting intrauterine manipulations with greater safety and less possibility of rupture of the lower uterine segment.

Various authors have reported delivering the second twin by means of forceps, past the neck and body of the breech, if the heads are locked deep in

the pelvis. If the pelvis is large, it is possible in some cases to deliver the infants in a locked position using forceps on the second infant's head as described above.[7]

It may be necessary to decapitate the breech twin, disengage the heads, deliver the second twin, and then allow the severed head to be delivered spontaneously.

True locking occurs only during the process of delivery and therefore cannot be treated by means of cesarean section if both infants are to survive. It is best handled by one of the above described methods. If a contraction ring develops, it might be necessary to perform a cesarean section. Such a case has been reported by Williamson.[4] Cesarean section is the procedure of choice in collision diagnosed during labor.

I wish to express my appreciation to Dr. J. H. Randall for his interest and suggestions in the preparation of this paper; to Drs. W. C. Keettel and William Goddard for permission to report their case of collision.

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OCCURRENCE OF A HYDATIDIFORM MOLE IN TWIN PREGNANCY

Case Report

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CASES in which a typical hydatidiform mole coexists with a normally developed fetus are rare. Bland[2] has expressed the opinion that the presence of a well-developed fetus and an advanced mole in the uterus at the same time would seem physically impossible, except in a plural pregnancy. Fewer than a dozen cases have been reported in the entire literature. A review of a series of 71 cases of hydatidiform mole at the Woman's Division of St. Luke's Hospital over a period of 26 years (1929–1955) disclosed one case prior to the present report. This was a spontaneously delivered normal fetus of 18 weeks' gestation with a normal placenta and an accompanying mole. Similar cases[3, 8, 11, 12] have been reported in the literature. Other investigators[1, 6, 13] have recorded cases of living normal fetuses coexisting with moles.

The present case, which emphasizes certain interesting features, is presented in order to augment the existing collection of cases of hydatidiform mole occurring in multiple pregnancy.

A 24-year-old woman, complaining of nausea, vomiting, and epigastric pain of one week's duration, was first seen on Oct. 1, 1950. The patient, who had been married on Sept. 15, 1950, reported that her last menstruation was on Aug. 22, 1950. According to her menstrual cycle, she was 10 days late with her next period.

Examination showed a petite woman of Chinese nationality in good physical condition. The uterus was slightly enlarged and softened in consistency. A tentative diagnosis of pregnancy was made, which was confirmed at the next examination, two weeks later.

Throughout the first trimester of pregnancy, there was pronounced nausea and vomiting. The patient did not respond readily to oral and parenteral administration of vitamins, sedatives, and antispasmodics. On December 20, during the eighteenth week of gestation, she noticed for the first time a slight vaginal staining which persisted for four days. One week later the patient was admitted to Woman's Hospital in acute distress. She was found to be acutely ill, dyspneic and toxic, with generalized and marked edema of the face, extremities, and abdomen. Since her examination one week earlier, the abdomen had enlarged to the size of a full-term pregnancy. The diagnosis was acute hydramnios, resulting from a possible hydatidiform mole or multiple pregnancy.

Studies showed a marked secondary anemia with 6.2 Gm. of hemoglobin per 100 ml. blood and 2.2 million red blood cells. X-ray of the abdomen showed a small fetal skeleton of about 18 weeks' gestation. It was the impression of the roentgenologist that there was an associated large ovarian cyst, although ascites and hydramnios could not be ruled out.

It was decided to terminate the pregnancy by hysterotomy. The uterus was found to be acutely distended with amniotic fluid and to contain a twin pregnancy. One fetus, of about 4 months' gestation, was apparently normal in development, with the umbilical

cord attached to a normal-appearing placenta. The rest of the uterine cavity was filled with extensive grapelike clusters of cystic vesicles resembling a typical hydatidiform mole. The specimen was interpreted as a normal fetus of 16 weeks with a second-trimester placenta, to which a hydatidiform mole was intimately attached.

Quantitative Aschheim-Zondek tests, performed at intervals of two days and one week after the operation, were positive at 1:1,000 dilution. Quantitative Aschheim-Zondek assays repeated one month later and every three months thereafter for one year were negative. X-rays of the chest revealed no evidence of intrathoracic pathology.

Two years after operation, the patient was delivered by cesarean section of a healthy 6 pound, 3 ounce boy. When last seen, five years after delivery of the mole, she was in good physical condition.

Comment

The etiology of hydatidiform mole is not known but the primary defect is thought to originate in the ovum. In a twin pregnancy, one embryo becomes a hydatidiform mole while the other develops normally. Hydatidiform changes are not infrequent in early pregnancy but as the pregnancy advances these changes become more uncommon.

In the early stages of a mole in twin pregnancy, there are no characteristic clinical features that will permit diagnosis. Uterine bleeding is the outstanding symptom and is usually interpreted as threatened or incomplete abortion. Diagnosis is usually made after the specimen has been expelled, or during curettage. If early abortion does not occur, uterine bleeding may persist for weeks, or perhaps months, and be mistaken for a missed abortion. In a patient with persistent bleeding, a uterus larger than the expected size suggests the presence of a mole in twin pregnancy. Contrary to other reports in the literature, I have found that the uterus was enlarged out of proportion to its period of gestation in less than one fourth of the cases studied.

There is general agreement that hyperemesis gravidarum often occurs during the first trimester; toxemia and pre-eclampsia frequently arise in the second trimester; and hemorrhage and infection are the most common complications. The most serious risk is malignant transformation of the mole to a chorionepithelioma and one must be constantly alerted to this possibility.

Treatment is directed first to immediate abortion or evacuation of the mole; and, second, to follow-up quantitative Aschheim-Zondek assays for detection of a chorionepithelioma. In the majority of cases, abortion is imminent and spontaneous. Hemorrhage and infection are combated with blood and chemotherapy. A careful curettage is recommended in every case before the patient is discharged, in order to obviate confusion in clinical and Aschheim-Zondek follow-up. Retained secundines may give rise to positive tests for chorionic gonadotrophins, which could erroneously be interpreted as new growths.

In the case of a mole, with no sign of impending abortion and a uterus enlarged to the umbilicus or above, hysterotomy is the safest treatment. The evacuation of a large mass through an undilated cervix entails considerable risk of hemorrhage and trauma. If an abdominal approach is necessary in a

woman with several children, or in one approaching menopause, hysterectomy is the operation of choice, as it meets the immediate problem and minimizes the risk of future malignancy.

It is recommended that quantitative Aschheim-Zondek tests be performed weekly until the results are negative, and then monthly thereafter for one year. In about 10 per cent of the cases, there is a persistent elevation of chorionic gonadotrophins, or rising titer. Repeated curettage is indicated in these cases. It is important to bear in mind, however, that negative findings on curettage may be misleading, as the trophoblasts sometimes lie deep in the myometrium, beyond the reach of the curette. Hysterectomy is indicated in the presence of any new or active growth.

Summary

A report is presented of a rare occurrence of a twin pregnancy, in which a well-developed fetus occurred in conjunction with a hydatidiform mole. Acute hydramnios necessitated termination of the pregnancy by hysterotomy.

A five-year follow-up of the patient showed no evidence of the recurrence of the disease or of malignant transformation.

This case is one of 71 cases encountered at the Woman's Division of St. Luke's Hospital over a period of 26 years.

I wish to acknowledge with thanks the editorial assistance rendered by Mrs. Rose M. Schweitzer, Editor for Clinical Research, Roosevelt Hospital, and the laboratory assistance rendered by Dr. Leon Motyloff, Pathologist of Woman's Division of St. Luke's Hospital.

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PROLAPSE OF THE CERVIX IN PREGNANCY

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SINCE frank prolapse of the cervix in pregnancy is rarely encountered, we are presenting a case in which repeated prolapse was noted with successive pregnancies.

Eastman[1] stated that the condition of abnormal elongation seriously interferes with conception but usually does not complicate the course of pregnancy or labor. Its severest degree of extension was in the first trimester; the cervix usually retracts as pregnancy advances, rarely continuing to protrude from the vulva.[2] Even less frequently, the cervix becomes so edematous at delivery as to necessitate multiple incisions to allow delivery.

A moderate degree of prolapse may, with venous obstruction exaggerated by the strain of defecation, lead to acute edema of the cervix. The cervix is extruded out of the introitus, producing in a matter of hours, with more obstruction, a tense edematous, external mass.[2]

In the older literature, there are reports of frank prolapse of the cervix, years in duration, complicating the course of several pregnancies in the same patient, viz., Jardine,[3] Truman,[4] and Warren.[5]

The exposed cervix and vaginal walls become the sites of considerable edema and ulceration with profuse vaginal discharge if untreated. Pessary support is ill advised, as sepsis invariably results.[2, 6] Complete bed rest for the first trimester, with one to two days per week thereafter, is the treatment of choice.

A case report follows in which it was observed that virtually complete bed rest throughout pregnancy should have been the bulwark of treatment.

Case Report

Mrs. N. C. J., a white 32-year-old, para iii, gravida vii, was admitted to the 2275th USAF Hospital on October 5, approximately one week past her expected date of confinement of Sept. 29, 1955, for observation on bed rest. The pertinent finding was a large, swollen, reddish-blue, eroded, easily bleeding cervix protruding 4 cm. outside the vulva with the patient standing erect. A moderate degree of foul discharge was present. The fetal heart tones were good, as was the patient's general condition. The size of the uterus was consistent with the history of a pregnancy at term. The head was fixed in the pelvis.

The patient's past history of note went back to 1944, with her first pregnancy, complicated by pyelitis, an 80 pound weight pain, and two eclamptic convulsions. The patient was delivered 48 hours after the second convulsion of a living male child that weighed 9 pounds.

In 1947, right nephropexy and ureteroplasty were performed, followed by a course of multiple bladder irrigations in treatment of recurrent cystitis. At this time, though asymptomatic, she was first told of the presence of a mild uterine prolapse.

In 1949, the patient had a term pregnancy and normal delivery, complicated only by right pyelitis.

In 1950, an abortion at 4 months was treated by curettage. It was during this pregnancy that the patient first noted prolapse of the cervix outside the introitus, accompanied by bleeding and pain. With involution, retraction of the cervix took place. Mild discomfort with coitus was noted from here on.

In 1952, she had a term gestation and uneventful delivery. No frank prolapse of the cervix was noted with the pregnancy.

In 1953, she again aborted, at about 2 months, and was curetted, followed by a transfusion, after considerable difficulty with the frankly prolapsed cervix. Three months after curettage (May of 1953) an abdominal uterine suspension was performed, with poor results. The hypertrophied cervix could be easily felt far down in the vaginal canal, giving rise to pain with coitus and occasional postcoital spotting.

In early 1955, with her seventh pregnancy, she again noted complete prolapse of the cervix, with spotting, midway between the times of the first and second missed periods. She was first seen at the prenatal clinic of the 2275th USAF Hospital on March 18, 1955. Her weight was 124½ pounds, height 5 feet, 3½ inches, and the blood pressure was 122/60. Examination disclosed a gaping introitus, a relaxed perineum with moderate cystocele and rectocele, a fairly extensive annular erosion of the cervix, and a uterus enlarged to the size of a 3 months' gestation. No mention was noted of the degree of cervical prolapse.

On May 13, 1955, the patient was admitted to Letterman Army Hospital in the sixth month of gestation. She was placed on a regimen of absolute bed rest, marked Trendelenburg position, and daily vaginal instillations of Triple Sulfa Cream. On June 30, 1955, after marked improvement, a molded Smith-Hodge No. 5 pessary was fitted and placed in the vagina in reverse, so as to impinge upon the anterior portion beneath the neck of the bladder. Upon leaving Letterman Army Hospital, she was advised to continue the pessary and sulfonamide cream instillations until near term.

Her course during the next three months was relatively unsatisfactory. Because of the profound degree of perineal relaxation present, the pessary did not maintain the uterus in place, on full ambulation. Again it became necessary for her to spend much time in bed.

An x-ray on Oct. 5, 1955, disclosed that the fetal distal femoral epiphyses were present. Vaginal examination showed the cervix to appear no worse than it had for several weeks, to be very soft, and, apparently, easily dilatable. The vertex presented, the head fixed in the pelvis. Accordingly, on October 6, medical induction of labor with intravenous Pitocin drip (1 ampule of Pitocin to 1,000 c.c. of 5 per cent dextrose solution) was attempted, in an effort to have labor proceed while the senior author was present. The procedure failed to bring on labor after a reasonable try of 3½ hours.

During the next 12 days, on virtually absolute bed rest (and sulfonamide cream) a marked improvement in the appearance of the cervix took place, with almost complete disappearance of vaginal discharge.

On October 18, 1955, a labor of 3 hours and 34 minutes resulted in easy spontaneous delivery of a 6½ pound female infant. After delivery, the cervix appeared to be intact, firm, and to present lips only slightly thicker than those normally seen immediately post partum. The remainder of the hospital stay was normal, the mother and child being discharged on the fourth postpartum day.

At six weeks post partum, on vaginal examination, the firm, well-involuted, moderately thickened, mildly eroded cervix descended to within 2 cm. of the introitus on straining.

On Dec. 9, 1955, the patient was readmitted to the 2275th USAF Hospital for a combined procedure including tubal ligation, Manchester operation, and an extensive perineal repair. Hysterectomy had been refused.

Following the operation, her course was uneventful, leading to discharge on the eleventh postoperative day.

Comment

Quite apart from the situation usually recorded, the patient had little difficulty conceiving in the face of a considerable degree of occult prolapse.

Her failure to be bothered by abnormal elongation in her fifth gestation, after difficulty with the immediately preceding pregnancy, has no obvious explanation.

Little change for the better was noted during the current pregnancy, despite accounts in the literature of spontaneous improvement which usually occurs once the patient is past the first trimester.

Certainly, bed rest profoundly affected the patient's comfort, as well as the appearance of the cervix whenever the regimen was enforced with hospitalization.

The use of a pessary in treatment of frank prolapse of the cervix in pregnancy appears to be of little value.

Summary

A case of rank prolapse of the cervix in pregnancy has been reported. Almost continuous bed rest may be the treatment of choice.

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Editorial

Blood Tests to Determine Whether Uterine Cancer Has Been Cured

No one knows until a complete autopsy has been performed whether or not a cancer was cured one, five, ten, or more years previously. All methods of treatment are based on arbitrary survival periods of five, ten, or more years. Major pelvic surgery entails a relatively high mortality compared to irradiation treatment and yet every gynecologist who has treated uterine malignancy either by irradiation or by the radical hysterectomy and lymphadenectomy always has patients in whom he wished he had made a more extensive operation or given more irradiation treatment. The operation would have increased the mortality slightly and greater irradiation would have increased the likelihood of fistulas or of injury to bowel. Most gynecologists and radiologists forget one very important fact: the patient gambles her all. She should be treated intensively while there is still a chance for eradication. If the cancer of the cervix or of the endometrium is not completely removed by surgery or destroyed by irradiation in the first period of treatment, by the time a recurrence either local or distant becomes evident, so much time has been lost that the cancer is now widespread.

The Editor has had the hope for several decades that some test could be devised or, if already available, could be properly interpreted in order that the gynecologist would know within four to six months after either surgery or irradiation that he had cured the cancer of the uterus or that living cancer cells were still growing somewhere in the body.

Tests to determine the presence or absence of enzymes in the blood were first reported early in this century[9, 10] and were based at first on the Abderhalden reaction, about which much has been written, some by investigators with insufficient vision. A number of reports thereafter helped to conceal the possibilities inherent in these cancer tests. Some of these investigators claimed that, with extracts of liver, kidney, brain, uterus, or ovary and a sample of the patient's blood, they could tell not only in which organ there was cancer but also whether it was a carcinoma or sarcoma. Obviously, these claims could not be substantiated.

I have read the reports of over 50 different tests to detect the presence or absence of cancer and have tried 8 of them. I have found no tests to be completely reliable. There have been false positives and false negatives, but are these the result of a faulty test or a faulty interpretation? I recall one doctor's mother in whom several cancer tests were consistently positive for malignancy, but a complete pelvic examination, x-ray of the lungs and of the gastrointestinal tract by a competent internist and roentgenologist were negative.

Yet, when the patient died a year later from a coronary thrombosis, scirrhous-cell carcinoma of the stomach was found. No one can state how long it had been present.

The article by Kahn and associates in this issue represents several years' intensive work by the senior author and some two years' work under his supervision in the department of obstetrics and gynecology at the Chicago Lying-in Hospital. The test showed promise but when we found that we had some false negatives, we deemed the test would not detect whether or not cancer had been cured. The senior author has continued his study and now believes he has improved the test to such a degree that it will function as we believed such a test should, namely, give information within 4 to 6 months after the uterine cancer has been properly treated as to whether or not living cancer cells are still present in the patient's body. All of these tests are used to determine the presence or absence of cancer. No one has used any of these tests, as I envision, to determine when the cancer has been cured. This should simplify the problem for the positive test would then become negative.

Periodically, there is increased interest in tests for cancer as evidenced by an increased number of reports and reviews.[1-8, 11-19]

At present, no test is specific for the presence or absence of malignancy. It is possible, however, that too much has been demanded of such a test. Some tests[4, 14, 16] have been reported to be of value for screening patients.

An extremely valuable contribution would be the evaluation of those tests which have the lowest false negative rate to determine whether or not the cancer had been cured.

W. J. D.

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Reviews and Abstracts

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Review of New Books

Williams Obstetrics. By Nicholson J. Eastman. Eleventh edition. 1212 pages with illustrations and tables. New York, 1956, Appleton-Century-Crofts, Inc. $14.00.

The appearance of a new edition of *Williams Obstetrics* is a singular event in American medicine. From the dedication to all the residents and interns who served on the obstetric service at Johns Hopkins Hospital to the very end of the book it is packed with scientific and clinical information which provides the basis for our specialty. A textbook which has passed through many editions often accumulates much dated and obsolete material. However, in this eleventh edition the author has eliminated most of the extraneous material that the advances in our knowledge have proved to be faulty or worthless; he has retained accepted scientific data and sound clinical practice; and he has added all that is new and promising that pertains to the field of human reproduction.

A marked change has occurred in our specialty, for our practice of obstetrics has become more and more standardized, whereas the science of obstetrics has made great strides in recent years. The minutiae of a normal or an operative delivery may vary considerably in different institutions but as long as basic principles are respected the results for mothers and babies will be safeguarded. This volume emphasizes this important change in our approach to obstetric practice and teaching.

The spectacular reduction in maternal and perinatal mortality has made it possible to place increased emphasis on the emotional factors in human reproduction. This approach is emphasized in the excellent chapter on the psychiatric aspects of pregnancy and childbirth by Leo Kanner. In a most informative and delightful manner he stresses the importance of human behavior at the most important period in life and interprets anxieties and uncertainties in the light of human emotions. This chapter can serve as a background for our increased emphasis on parent education.

It is not the purpose of this review to detail the many changes and additions in this new edition. Suffice it to say that many sections have been rewritten completely, for much scientific and clinical progress have been made in these areas. Obstetric shock and fibrinogenopenia are discussed in the chapter on abruptio placentae and placenta previa. Sections on such subjects as habitual abortion, postmaturity, placentography, retrolental fibroplasia, water, calcium and iron metabolism, uterine blood flow, and others have been rewritten completely.

The author, who is a keen student of English usage as well as of obstetrics, introduces two new terms which he hopes will find universal acceptance. The term lie replaces presentation, for the latter has always been confused with presenting part. Antepartal is used for prenatal. It is the reviewer's impression that it will take a new generation of obstetricians to popularize these logical changes in terminology.

Many individuals have helped in the revision of this textbook and their combined efforts have produced this classic volume. Dr. Bartelmez in the revision of embryology, Dr. Georgeanna Seeger Jones on endocrinology, Dr. Leon C. Chesley on the toxemias, Dr.

Alan F. Guttmacher on multiple pregnancy, and a number of other teachers have helped in the preparation of this revision. However, the author singles out Dr. Louis M. Hellman for his help and guidance throughout the rewriting of this book.

The reviewer takes this opportunity to congratulate the author for his noteworthy contribution in presenting another edition of *Williams Obstetrics,* written in a delightful manner, profusely illustrated by new and old pictures, diagrams, and tables, and containing well-chosen bibliographies. This book should be read by every medical student, all physicians who are remotely interested in human reproduction and, of course, the specialists in our field.

M. EDWARD DAVIS, M.D.*

Handbook of Pediatric Medical Emergencies. By A. G. DeSanctis, and C. Varga. Second edition. 389 pages with 72 figures. St. Louis, 1956, The C. V. Mosby Company. $6.25.

It is a widespread custom in pediatric clinics to have guides available for reference in the event of medical emergencies. These guides vary from brief statements of policy to comprehensive coverage of pediatric emergencies, although the latter is rarer by far. This is partly because of the effort required in preparation of comprehensive manuals, but also simply because standard pediatric textbooks contain most of the information which might be assembled in such compendiums.

When such guides become available, however, they are exceedingly popular. Witness the fact that four printings of the first edition of this book were exhausted within four years. The second edition will no doubt be similarly received. New chapters on metabolic emergencies, accident and poison prevention, genitourinary emergencies, and respiratory paralysis in poliomyelitis have been added to the previous list consisting of cardiovascular, neurologic, respiratory, and miscellaneous emergencies. The last covered such varied problems as epistaxis and pediatric anesthesia. A comprehensive and well-illustrated chapter on pediatric procedures is included.

Nurse-Patient Relationships in a Hospital Maternity Service. By M. S. Lesser and V. R. Keane. 301 pages. St. Louis, 1956, The C. V. Mosby Company. $4.25.

This book focuses attention upon changing obstetrical concepts and demands. Although statistics show that with better obstetrical care available today to the majority of women there has been a constant decline in the physical hazards of childbearing, much remains to be accomplished in satisfying emotional, intellectual, and informational needs of maternity patients. The purpose of this work is to examine obstetrical nursing in respect to its fulfillment of the needs and expectations of maternity patients, and to examine prevalent obstetrical nursing theory in this light. Information was gleaned by interviews.

Some of the barriers to improved nurse-patient relationships stem from the shortage of personnel. Nurses, assigned to one of several areas of maternity care, focus their attention on areas of work rather than on individuals. Not only is there "segmented care," but also there are specific assigned areas within each segment. This makes for routinization of the job. While many nurses consider the chief functions of nursing to be those which are medical, patients value these functions least. Although caring for the patient's bodily needs has always been conducive to the development of meaningful nurse-patient relationships, today this duty is assigned to auxiliary personnel. The average nurse fails to recognize and cope with the patient's needs because of her limited knowledge or ability.

To correct the existing defects, the nursing profession must re-evaluate its functions in maternity care. It must decide whether or not priority should be given to technical

*Because the editor of Reviews and Abstracts aided in the rewriting of *Williams Obstetrics,* an exception has been made to the editorial policy in regard to the signing of book reviews.

functions. If the objectives of nursing are to be broadened, hospitals must provide improved facilities, and patients and nurses must be more thoroughly informed.

Pelvimetry. By Herbert Thoms. 120 pages with 45 figures. New York, 1956, Paul B. Hoeber, Inc. $5.00.

This book is a condensation of Dr. Thoms' many contributions to obstetric literature on pelvimetry. It contains 16 short chapters which superficially cover many phases of pelvimetry and treat none exhaustively. The author's aim in writing the book is to "confine the text chiefly to the practical aspects of the subject as viewed for the most part through . . . [his] own experience." Because of this there is no reference to methods of pelvimetry other than that of the author, there is no bibliography, and there is no recognition of pelvic classification used by almost everyone else. The suggestion of a single-film "screening technique," previously suggested in a recent issue of the *J. A. M. A.*, is repeated. The experience of many clinics where pelvimetry is a supplement to clinical evaluation indicates that pelvimetry is not used or indicated in all patients.

Textbook of Gynecology. By Emil Novak and Edmund R. Novak. Fifth edition. 840 pages with 543 illustrations. Baltimore, 1956, Williams & Wilkins Company.

The fifth edition of the *Textbook of Gynecology* by Novak and Novak has been received for review. The increased number of reprintings for successive editions (two of the third, 1948, and four of the fourth, 1952) is evidence of the growing popularity of the text. This has been richly deserved because of the marked improvement of each edition over the preceding one.

Better than any other American text, this book has presented a comprehensive view of modern gynecology, stressing description, symptomatology, and diagnosis of gynecologic disease. The presentation of pathology has been succinct and accurate with fine illustrative material. Emphasis has been placed on medical rather than surgical aspects of treatment. While the medical phase of gynecology has come increasingly to the fore with the advent of purified hormones and antibiotics, the day is not yet here when surgery can be treated as superficially as it is in this text without sacrificing the understanding of certain essental principles. Furthermore, Novak has glossed over, if not omitted outright, important statistical data, perhaps thereby unconsciously reflecting his distaste for this aspect of human biology.

The fifth edition is no exception to the others, and merits much of the same praise and some of the criticism. The book has been expanded by 41 new pages and new and better illustrations have been either added or substituted. References for the most part have been brought up to date and appropriate changes have been made in the text. However, in the last chapter, "Urinary Disorders," a text published in 1940 by Langworthy is still referred to as recent. Also in this chapter Jeffcoate's work is mentioned without a reference and Ullery's name is misspelled. This certainly reflects a none-too-thorough revision of the chapter.

The previously mentioned omissions of statistics are still apparent. Thus, while malignant change in pseudomucinous cyst is given a 5 per cent incidence, the same change for serous cyst is referred to only as "much more common." Similarly, while various sorts of rates are mentioned in regard to the occurrence of cervical carcinoma, the age specific occurrence rate is not given. This renders less meaningful the discussion which follows on cervical carcinoma in nuns. The omission of a discussion of surgical principles in "Perineal and Vaginal Relaxations and Urinary Tract Disorders" is a real deficit.

On the other hand, the chapter on "Carcinoma of the Uterus" is one of the finest in the book. Reflecting as it does a long-standing interest of the senior author, by its all-encompassing brevity it clearly portrays the breadth of his knowledge.

The format is excellent, the print pleasing and easy to read, the illustrations exceedingly well produced, and the index adequate.

Selected Abstracts

The American Journal of the Medical Sciences

Vol. 232, August, 1956.

Bello, C. T., and Turner, L. W.: Reserpine as an Antihypertensive in the Outpatient Clinic: A Double Blind Clinic Study, p. 194.

Bello and Turner: Reserpine as an Antihypertensive in the Outpatient Clinic, p. 194.

Twenty-five patients with mild to moderate hypertension were selected at random from the Hypertension Clinic. The age range was from 31 to 73 years; all but 2 were women; 17 were Negro and 8, white. In all cases, renal, neoplastic, and endocrinologic causes of hypertension had been excluded. Patients given reserpine received 0.2 mg. three times a day in one group and 0.5 mg. three times a day in the second group. A third group received a placebo on the same schedule, and a fourth, untreated, served as controls. All patients were examined once a week for five months. About two-thirds of the patients on reserpine treatment had side effects, such as muscular aches and pains, stuffiness of the nose, drowsiness, headaches, nausea and vomiting (in that order of frequency).

Reserpine had no significant effect on the pulse rate or blood pressure of patients treated in the outpatient clinic.

LEON C. CHESLEY

Vol. 232, September, 1956.

Caccamo, L. P., Pringle, B. H., and Hissong, D. E.: A Therapeutic Evaluation of the 1-Allyl-3-Ethyl-6-Aminotetrahydropyrimidinedione (Mictine), a New Oral Diuretic, p. 289.

Caccamo, Pringle, and Hissong: A Therapeutic Evaluation of Mictine, a New Oral Diuretic, p. 289.

Sixteen edematous patients with either cardiac failure or cirrhosis were studied. After a three-day control period on a 200 mg. sodium diet, Mictine was given orally, 0.5 Gm. with each meal for three days; water was allowed as desired. A good response in urine output, sodium loss, and weight loss was obtained in 69 per cent. The average fluid loss (intake minus urine output) was 590 ml. per day, the average weight loss was 0.96 pound per day, and the average sodium loss was 34.6 meq. per day. There was no excessive loss of potassium. Severe nausea occurred in 18 per cent, 12 per cent having to stop taking the drug. Prolonged use or repeated courses of the drug increase the tendency toward nausea and vomiting.

LEON C. CHESLEY

The American Journal of Surgery

Vol. 92, July, 1956.

Collins, J. H., Burman, R., and Mathews, N.: Surgery for Carcinoma of the Vulva, p. 92.

Collins, Burman, and Mathews: Surgery for Carcinoma of the Vulva, p. 92.

Treatment of carcinoma of the vulva is generally surgical. Dr. Collins studies each afflicted patient by means of a diagnostic survey; a planned pre- and postoperative regimen; a fairly standardized method of surgical attack; histologic studies of tissues removed and follow-up studies. Further description of the surgical technique involved is presented. Treatment is by wide total vulvectomy; additional bilateral inguinal and pelvic lymphadenectomy is performed in cases of invasive carcinoma.

ROBERT KNAPP

Boletin de la Sociedad de Obstetricia y Ginecologia de Buenos Aires

Vol. 35, August, 1956.

Foix, A., Coll, A., and Iparraguirre, B.: The Protamine Titer in Functional Metrorrhagia and Treatment With Toluidine Blue, p. 229.

Foix, Coll, and Iparraguirre: The Protamine Titer in Functional Metrorrhagia and Treatment With Toluidine Blue, p. 229.

The circulating blood level of protamine, measured by the technique of Allen, was found to be elevated in 16 of 46 women with functional metrorrhagia and in 2 of 9 with organic metrorrhagia from myomas.

Sixteen women with functional metrorrhagia, 8 with abnormal titers and 8 with normal titers, were treated with toluidine blue. In 5 with abnormal levels, the clinical and hematological response was good. In all others, there was no response noted. The authors conclude that in cases of functional bleeding, if the protamine level is elevated, toluidine blue can be of benefit.

FRANCIS B. O'BRIEN

Die Medizinische

Vol. 44, November 3, 1956.

Catel, D. W.: Congenital Absence of the Ovaries, p. 1557.

Catel: Congenital Absence of the Ovaries, p. 1557.

This is the report of a 14-year-old girl with normal external genitals but no menarche; dysplasia of the left acetabulum; scoliosis; abnormal pigmentation of the body and of the fundus oculi. Urinary FSH was high and vaginal smear showed a definite follicular hormone effect. Laparotomy revealed no definite ovaries but definite strands of tissue which included some ovarian stromal and hilus cells. The uterus, tubes, and round ligaments were rudimentary. The vagina was 6 cm. long. The urinary excretion of free corticoids was 349, 497, and 362 gamma per day; excretion of 17 ketosteroids was 4.75, 6.06, and 6.10 mg. per day. Blood cytology showed male sex morphology. The author attributes the rudimentary uterus to a high estrogen level in utero from the placenta. Because of the absence of this source after birth, no further development occurred. Cyren-A administered to the patient effected the development of female secondary sex characteristics and improved her psychic outlook.

FRANCIS B. O'BRIEN

Ginecologia y Obstetricia de Mexico

Vol. 11, July–August, 1956.

Medina, H. M.: Considerations of Some Endocrine Factors Related to the Radiosensitivity of Cervical Carcinoma, p. 295.

Medina: Considerations of Some Endocrine Factors Related to the Radiosensitivity of Cervical Carcinoma, p. 295.

The author evaluated the vaginal smears of 68 patients with cervical carcinoma, with respect to the presence of S.R. cells as described by Graham. The criteria were easily observed, but the appearance of S.R. cells was related to estrogen levels, and the number of S.R. cells was increased by administration of testosterone. Dr. Medina does not feel that his sample is large enough for reliable evaluation and, therefore, further study is necessary.

FRANCIS B. O'BRIEN

The Journal of the American Medical Association

Vol. 160, February 11, 1956.

Thoms, H., and Billings, W. C.: Technique for Routine Pelvimetry With Use of Single X-ray Film, p. 448.

Thoms and Billings: Technique for Routine Pelvimetry With Use of Single X-ray Film, p. 448.

Although manual methods alone cannot be relied upon for screening the pelvic capacity of primigravid women, complicated x-ray pelvimetry is not essential for screening purposes. Careful manual evaluation plus a single roentgenogram can furnish adequate information so that pelves which deserve closer diagnostic study can be discovered. Pelves can be separated into two groups: those of adequate capacity for normal infants at term, and those whose capacity should receive further study.

DAVID P. BAUER

Vol. 160, March 10, 1956.

Moyer, C. A., and Key, J. A.: Estimation of Operative Risk in 1955, p. 853.

Moyer and Key: Estimation of Operative Risk in 1955, p. 853.

Comparison of figures of operative mortality 20 years ago with those for the last decade shows a marked decline, particularly for the aged patient. The difference in operative risk for most procedures is now insignificant. The duration of physiological stress to which the patient has been subjected is of more importance in determining operative risk than is the magnitude of the procedure contemplated, but this is difficult to evaluate. A very important factor in estimating operative risk is the surgeon's skill. The importance of other factors has become so insignificant as to warrant a reappraisal of the present surgical mortality rates.

DAVID P. BAUER

The Journal of Clinical Endocrinology and Metabolism

Vol. 16, September, 1956.

Raab, W., Schroeder, G., Wagner, R., and Gigee, W.: Vascular Reactivity and Electrolytes in Normal and Toxemic Pregnancy, p. 1196.

Briggs, D. K., and Kupperman, H. S.: Sex Differentiation by Leukocyte Morphology, p. 1163.

Briggs and Kupperman: Sex Differentiation by Leukocyte Morphology, p. 1163.

Neutrophils of 46 controls and 87 patients attending the endocrine clinic were studied to determine whether or not the presence or absence of "drumsticks" could be an aid to classifying sex variants.

Patients who had 6 "drumsticks" per 500 neutrophils were considered to be females. Normal males and females conformed completely, and sex variants conformed with a high degree of accuracy.

Studies should be carried out to correlate the chromosomal sex pattern with the leukocyte morphology.

J. EDWARD HALL

Raab, Schroeder, Wagner, and Gigee: Vascular Reactivity and Electrolytes in Normal and Toxemic Pregnancy, p. 1196

In general, the tonus of the arterial walls is determined by the catecho-amine content and by the adrenal corticoids which make the vascular cells responsive to the pressor catechol-amine action. An increase in intracellular sodium augments this action. Since there is an increase in corticoids in the last trimester of pregnancy, it is suggested that this may produce an increase in arterial muscle tonus by contributing to sodium retention.

The blood pressures of pregnant patients who had been given infusions of epinephrine and l-norepinephrine solution were recorded every minute for 5 minutes. In 100 cases of completely normal pregnancy in the last trimester there was no significant effect on the vascular pressor responsiveness; in 50 with edema, 24 with albuminuria, and 17 with hypertension, there was an increase of average vascular pressor reactivity.

The phenomenon of toxemic hypertension is interpreted as being caused by a corticoid-induced increase of the intra-extracellular cationic gradient, and by its potentiating effect upon vascular-cell contractility. The contractility is a response to the adrenosympathogenic pressor catechol amines and possibly also to other, as yet unidentified, pressor agents.

J. EDWARD HALL

The Lancet

Vol. 2, September 15, 1956.

Clayton, C. G., Farmer, F. T., and Johnson, T.: Transfer of Radiosodium to the Human Fetus in Late Pregnancy, p. 539.

Clayton, Farmer, and Johnson: Transfer of Radiosodium to the Human Fetus in Late Pregnancy, p. 539.

Preliminary observations obtained by measuring the fetal accumulation of radiosodium by means of a scintillation counter ingeniously applied to the mother's abdominal wall indicate that it is possible to obtain a measure of placental efficiency. In normal pregnancy, characteristic curves of uptake are obtained, depending upon the degree of obesity and other factors. When fetal death occurs, there is no accumulation of radioactivity. In pre-eclampsia, the uptake is much less than normal, and decreases as the condition grows worse. When repeated observations indicate a decreasing accumulation of radiosodium, insidious injury to the placenta may have occurred. If this warning is heeded, the incidence of intrauterine death may be reduced. Other applications of this method may appear as the method is developed.

DAVID M. KYDD

Vol. 2, September 22, 1956.

Jennison, R. F., and Walker, A. H. C.: Fetal Death in Utero With Hypofibrinogenemia, p. 607.

Jennison and Walker: Fetal Death in Utero With Hypofibrinogenemia, p. 607.

Eight weeks after fetal death occurred during the twenty-fourth week of pregnancy, presumably due to Rh incompatibility, the patient noticed spontaneous bruising. At that time the level of fibrinogen in the plasma was 76 mg. per cent and the prothrombin time was approximately twice normal. After the addition of fibrinogen, the prothrombin time became normal, and spontaneous hemorrhages became less and then ceased although the level of fibrinogen did not change. A test dose of 2 Gm. of fibrinogen caused a rapid rise

in the fibrinogen level in the plasma from 70 to 123 mg. per cent, but the level fell to below 100 mg. per cent in 12 hours and to its initial value in 24 hours. Four days after the expected date of delivery, labor was induced and a dead fetus was delivered. The loss of blood, estimated to be 850 ml. during delivery, did not cease until 6 hours after delivery. By repeated determinations of fibrinogen concentration in the plasma, it was found that there was no appreciable rise until 6 hours later (from 90 to 126 mg.). Thereafter, the concentration rose steadily, reaching about 240 mg. per cent in 36 hours, and 364 mg. per cent in 48 hours. Except for the test dose of fibrinogen, none of this substance or transfusions were given until 2 days after delivery.

DAVID M. KYDD

Vol. 2, October 27, 1956.

Jackson, W. P. U., Shapiro, B. G., Uys, C. J., and Hoffenberg, R.: Primary Male Hypogonadism With Female Nuclear Sex, p. 857.

Forrest, A. D., and Hales, I. B.: Severe Chorea Gravidarum Treated With Corticotrophin, p. 874.

Jackson, Shapiro, Uys, and Hoffenberg: Primary Male Hypogonadism With Female Nuclear Sex, p. 857.

This is the report of a 35-year-old male with primary hypogonadism. Urinary excretion of 17-ketosteroids was 5.6 and 7.3 mg. per day and FSH excretion was strongly positive at 48 mouse uterine units per day. The nuclear pattern of both skin and leukocytes was female. No evidence of hermaphroditism was found upon searching exploration of the patient's abdomen. The authors speculate as to whether or not this discrepancy may be explained by an early "sex evocator" which precedes the gonadal hormone and determines whether or not the primitive gonadal tissue becomes ovarian or testicular (Hoffenberg and Jackson: J. Clin. Endocrinol., 1957.

Two further instances of Klinefelter's syndrome have been studied and in both the nuclear sex was unquestionably male, indicating that not all patients with primary hypogonadism with eunuchoidism are chromosomal females.

DAVID M. KYDD

Forrest and Hales: Severe Chorea Gravidarum Treated With Corticotrophin, p. 874.

A married primigravida, without evidence of previous rheumatic disease, developed chorea early in pregnancy. As the chorea rapidly grew worse, she became maniacal and lost touch with her environment. Administration of corticotrophin was begun on the seventh day of her illness and continued for 3 weeks. The chorea improved steadily and disappeared after a week of therapy, with no recurrence. Six months later the patient was delivered of a normal male child. Neither at this time nor at an examination 2 months later was any evidence of cardiovascular or neurological abnormality found.

DAVID M. KYDD

Vol. 2, November 10, 1956.

Strong, J. A., Brown, J. B., Bruce, J., Douglas, M., Klopper, A. I., and Loraine, J. A.: Sex Hormone Excretion After Bilateral Adrenalectomy and Oophorectomy in Patients With Mammary Carcinoma, p. 955.

Strong, Brown, Bruce, Douglas, Klopper, and Loraine: Sex Hormone Excretion After Bilateral Adrenalectomy and Oophorectomy in Patients With Mammary Carcinoma, p. 955.

The excretion of total urinary estrogens (estradiol-17β, estrone, estriol), pregnanediol, 17-ketosteroids, and pituitary gonadotrophins was studied in 13 patients subjected to bilateral adrenalectomy and oophorectomy at intervals ranging from 6 weeks to 15 months after the operation. During the period of observation, 25 to 50 mg. of cortisone was given

daily with the exception of 1 to 1.5 mg. of 9 α-fluorohydrocortisone following bilateral adrenalectomy and orchidectomy. Clinical assessment by at least 2 observers classified the patients as 8 "successes" and 5 "failures" but the pattern of hormone excretion was the same in both groups. Measurable, though small, amounts of estrogens and pregnanediol were excreted by some of the patients after operation, but these amounts were not increased when corticotrophin was administered. The supposition is, therefore, that these substances are not being elaborated by any remaining adrenal tissue. This is further substantiated by the absence of any significant decrease in circulating eosinophils after corticotrophin is given. These patients ultimately succumb to a recrudescence of the tumor. The question is raised whether or not this is due to some change in the tumor itself, a hitherto undetected alteration in hormonal environment, or the influence of endocrine factors that were not considered in this study.

DAVID M. KYDD

Muenchener Medizinische Wochenschrift

Vol. 98, September, 1956.

Randerath, E., and Hieronymi, G.: On the Question of So-called Carcinoma in Situ, p. 1269.

Florian, J., and Wuerterle, A.: A Clinical Picture of Partial Pituitary Insufficiency, Post-partum, p. 1313.

Randerath and Hieronymi: On the Question of So-called Carcinoma in Situ, p. 1269.

From 1950 to 1956, 11,000 curettage specimens and 660 biopsies of the cervix were obtained for investigating the presence of carcinoma in situ. It was found in 0.2 per cent of the cases. Most of these specimens showed an "undifferentiated type." The age distribution varied between 26 and 80 years with the mode between 46 and 50. Invasive carcinoma was found with the same incidence. The relationship of carcinoma in situ to invasive carcinoma was 9.6 per cent. Comparing this figure with that obtained in other series, the authors conclude that the diagnosis of carcinoma in situ is made too freely. There is no proof that spontaneous regression occurs, or that carcinoma in situ is a preinvasive lesion. Only an experienced pathologist should make the difficult diagnosis. If there is only a small biopsy specimen available, it must be kept in mind that the lesion may be invasive elsewhere. Such lesions should be examined and followed further to rule out invasive carcinoma.

WALTER F. TAUBER

Florian and Wuerterle: A Clinical Picture of Partial Pituitary Insufficiency, Post-partum, p. 1313.

Cachexia was originally thought to be an invariable symptom of anterior pituitary insufficiency ("Simmond's cachexia"), but more recent observations have shown that nutritional status can vary anywhere from extreme emaciation to obesity. The main symptomatology of hypothyroidism, Addisonian picture and hypogonadism, is secondary to pituitary hypofunction. The early symptoms of postpartum pituitary failure, Sheehan's disease, are lack of milk and absence of menses. Treatment of Sheehan's disease lies in substitution therapy of hormones of peripheral glands, because adequate pituitary replacement is not possible at present.

Three cases are presented. The first is one of premature aging; the second, of myxedema; and the third, of spontaneous remission after severe endocrine disturbance.

WALTER F. TAUBER

Wiener Klinische Wochenschrift

Vol. 68, July, 1956.

Schueller, E.: The Value of Laboratory Examinations in the Diagnosis of Ectopic Pregnancy, p. 556.

Schueller: The Value of Laboratory Examinations in the Diagnosis of Ectopic Pregnancy, p. 556.

There are no unequivocal laboratory tests for establishing a diagnosis of ruptured tubal pregnancy. The presence of decidual tissue without chorionic villi is considered very useful information, but the risk from general anesthesia necessary for curettage militates against routine employment of this method. Positive results of biological pregnancy tests are helpful, but negative results by no means rule out the diagnosis.

Many tubal pregnancies are resorbed without significant intra-abdominal bleeding, but the possibility of dire results makes it impossible to treat patients inconclusively once the diagnosis has been made, and all efforts must be directed toward establishment of a definite diagnosis.

WALTER F. TAUBER

Wiener Medizinische Wochenschrift

Vol. 106, No. 35, September 1, 1956.

Rainer, A., and Szuka, Z.: Autotransfusion With Blood From the Peritoneal Cavity in Ectopic Pregnancy, p. 742.

Rainer and Szuka: Autotransfusion With Blood From the Peritoneal Cavity in Ectopic Pregnancy, p. 742.

Speedy transfusion is frequently a lifesaving procedure in ruptured ectopic pregnancy. Cross-matching takes much valuable time, so various methods of using blood from internal hemorrhage for transfusion have been tried since 1923. The present authors used a method described in 1928 by Knaus. The blood recovered from the abdominal cavity is filtered and transfused to the donor. By this method, 201 patients of 785 operated upon for ectopic pregnancy were transfused. The advantages were: lack of technical difficulty, obviation of transfusion reactions, quickness of availability, and economy in money and blood.

The following safeguards must be used: hemorrhaging must not have occurred more than 24 hours earlier and the patient must be afebrile with no evidence of pelvic inflammatory disease.

WALTER F. TAUBER

Books Received

The following books have been received. Selected reviews will appear in later issues.

Anatomy of the Trigonum Vesicae. By D. A. E. Norel. 239 pages. Nrjmegen, The Netherlands, 1956, Bekker & Van De Vegt N.V.

Bone Structure and Metabolism. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. 299 pages. Ciba Foundation Symposium. Boston, 1956, Little, Brown & Company. $8.00.

Colposcopy. By Hans Hinselmann. 48 pages with 38 illustrations. Wuppertal, Germany, 1955, W. Girardet. $4.50.

Diabetes Mellitus: Handbook for Physicians. By Howard F. Root and Priscilla White. 346 pages. New York, 1956, Landsberger Medical Books. $7.00.

Diseases of the Breast. By C. D. Haagensen. 751 pages with 404 figures, 25 charts. Philadelphia, 1956, W. B. Saunders Company. $16.00.

Diseases of the Heart. By Charles K. Friedberg. Second edition. 1161 pages with 157 illustrations. Philadelphia, 1956, W. B. Saunders Company. $18.00.

Heredity and Your Life. By A. M. Winchester. 333 pages. New York, 1956, Vantage Press, Inc. $5.00.

Histologischer Atlas gynäkologischer Erkrankungen. By Herbert Lax. 199 pages. Leipzig, 1956, Georg Thieme. 92DM.

Konservative Therapie der Frauenkrankheiten. By A. M. Müller. 42 pages, Vienna, 1956, Springer-Verlag. $7.50.

1956-1957 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill. 592 pages. Chicago, 1956, The Year Book Publishers, Inc. $6.75.

Observations on Krebiozen in the Management of Cancer. A. C. Ivy, J. F. Pick, and W. F. P. Phillips. 84 pages. Chicago, 1956, Henry Regnery Co. $2.50.

Paper Electrophoresis. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. 224 pages with 74 illustrations. Boston, 1956, Little, Brown & Company. $6.75.

Photokolposkopie und Photodouglasskopie. By Fredrick Menkan. 76 pages with 68 illustrations. Wuppertal, Germany, 1955, W. Girardet. $10.75.

Practical Office Gynecology. By A. Decker and W. H. Decker. 388 pages with 95 figures. Philadelphia, 1956, F. A. Davis Company. $10.50.

Items

American Board of Obstetrics and Gynecology, Inc.

The next scheduled Examinations (Part II), oral and clinical for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 16 through 25, 1957. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

Robert L. Faulkner M.D., Secretary
2105 Adelbert Road
Cleveland 6, Ohio

Clinical Fellowships of the American Cancer Society

The American Cancer Society announces that its program of Clinical Fellowships will continue through the institutional year July 1, 1958–June 30, 1959, with Fellowships commencing July 1, 1958.

Applications from institutions for the year 1958-1959 must be submitted by Deans, Executive Officers, or Department Heads prior to April 15, 1957. Note change in deadline from previous years.

Further information may be obtained from

Director of Professional Education
American Cancer Society, Inc.
521 West 57th Street
New York 19, N. Y.

Correspondence

Comment on "Uterine Hypertrophy in the Presence of Androgen-producing Adrenal Tumor"

To the Editors:

On page 206 of the January, 1957, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Drs. Quint, Parker, and Hamblen reported a case of "Uterine Hypertrophy in the Presence of Androgen-producing Adrenal Tumor." They were at a loss to account for the uterine hypertrophy, which unquestionably is a most unusual if not unprecedented feature. Having studied the action of androgen on the human uterus some years ago, I would say, however, that the uterine enlargement in their case is not surprising in view of the long duration of the tumor and its high level of androgen production.

The indirect effect of androgen on the uterus leading to atrophy of the endometrium is well known. This is brought about by anterior pituitary gonadotropic inhibition and consequent loss of ovarian function. Presumably less well known is the direct stimulation of the myometrium by the male hormone. Castrates receiving androgen therapy develop uterine contractions resembling those of the luteal phase of the menstrual cycle.[1] Similar contractions appear in women with normal ovarian function when subjected to suppressive doses of androgenic hormone.[3] The contractions apparently result from actual morphologic (hypertrophic) changes in the uterine muscle fibers since they do not appear until after several weeks of androgen therapy and they persist for more than a month after hormone therapy is discontinued.[1]

Increase or decrease in the size of the uterus was not observed in any of the women who received male hormone. In the majority of the cases, treatment lasted only a few weeks; one patient with endometriosis was kept on testosterone propionate for 13 months and received a total of 4,800 mg.[2] The patient described by Drs. Quint, Parker, and Hamblen had her tumor for 18 years and her urinary 17-ketosteroid levels were high.

Another direct androgenic effect, not mentioned in their case report, is the stimulation of the endocervical glands resulting in the copious secretion of clear, thin mucus with good *spinnbarkeit* similar to the cervical mucus associated with estrogenic activity. I have observed this type of mucus in patients under androgen therapy[2, 3] and in a case of arrhenoblastoma of the ovary.

LEO WILSON, M.D.

400 WEST END AVENUE
NEW YORK 24, N. Y.
JANUARY 15, 1957

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1. Wilson, L., and Kurzrok, R.: Endocrinology **26**: 587, 1940.
2. Wilson, L.: Endocrinology **27**: 29, 1940.
3. Wilson, L.: Obst. & Gynec. **4**: 97, 1954.

MENOPAUSAL SYMPTOMS

Crying Spells

Irritability

Excitability

Hot Flashes

Depression

Fatigue

Vallestril® in control of menopausal symptoms

"Relief of symptoms was observed in 91 per cent. . . ."[1]
". . . free of untoward effects."[2]

CLINICAL experience indicates Vallestril (brand of methallenestril) gives satisfactory results in more than 90 per cent of menopausal women and causes no significant side effects.

Goldfarb and Napp recently published[1] the results of a two-year study on Vallestril. They reported: "Relief of symptoms was observed in 91 per cent of the patients treated with methallenestril [Vallestril] and in only 15 per cent of those receiving placebos. No withdrawal bleeding or other untoward effects were noted in the patients receiving methallenestril. . . . A feeling of well-being was noted by the patients who responded to therapy."

According to these authors, "the great advantage of methallenestril lies in the absence of bleeding during therapy or on discontinuance of treatment with this drug."

Schneeberg and co-workers obtained[2] similar results. "Methallenestril (Vallestril) . . . induced satisfactory therapeutic results in 50 of 52 women with the menopause. . . . Methallenestril compared favorably with several other estrogens used in the treatment of the menopause and was free of untoward effects."

The average dosage recommended in the menopausal syndrome is 6 mg. daily for two to three weeks; thereafter, to control symptoms, 3 mg. daily as long as required.

Vallestril is supplied in scored, uncoated tablets of 3 mg. and 20 mg. Dosage for other indications is given in Searle Reference Manual No. 7. G. D. Searle & Co., Chicago 80, Illinois, Research in the Service of Medicine.

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1. Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Vallestril) in Control of Menopausal Symptoms, J.A.M.A. *161*:616 (June 16) 1956.
2. Schneeberg, N. G.; Perczek, L.; Nodine, J. H., and Perloff, W. H.: Methallenestril, a New Synthetic Estrogen, J.A.M.A. *161*:1062 (July 14) 1956.

SEARLE

EFFECTIVE WITHOUT COMPLICATIONS WITHIN 5 DAYS

Estan
Recommended dosage:[1]

3 tablets t.i.d. on the first 2 postpartum days,
2 tablets t.i.d. for the following 2 days, and
1 tablet t.i.d. for one day.

Virtually no breast engorgement, pain or induced vaginal bleeding[2,3] complicates the postpartum use of Estan in the recommended dosage. Well tolerated Estan is effective in relatively small oral dosage.

Supplied: In bottles of 30 and 100 scored tablets.

Estan
Other indications and dosages:

Menopause* or male climacteric—1 or 2 tablet daily.

Osteoporosis and senescence—1 or 2 tablets t.i.d. for 1-2 months, then 1 or 2 tablets per day.

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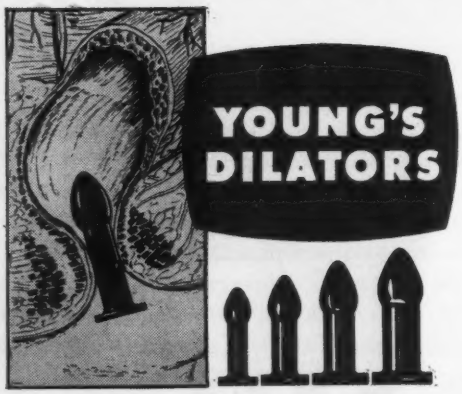

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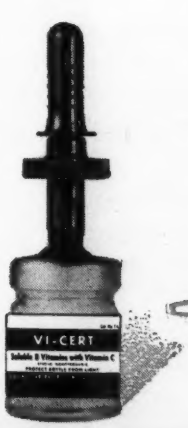

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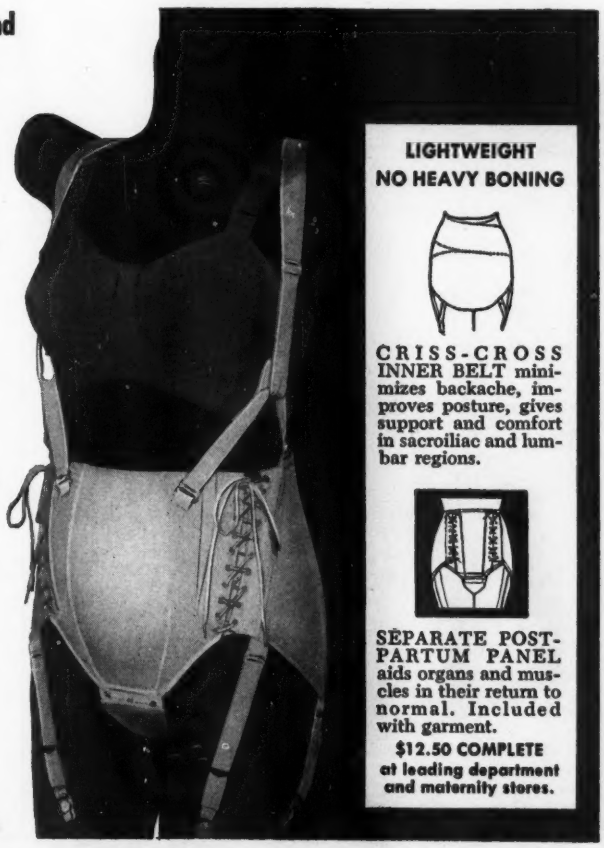

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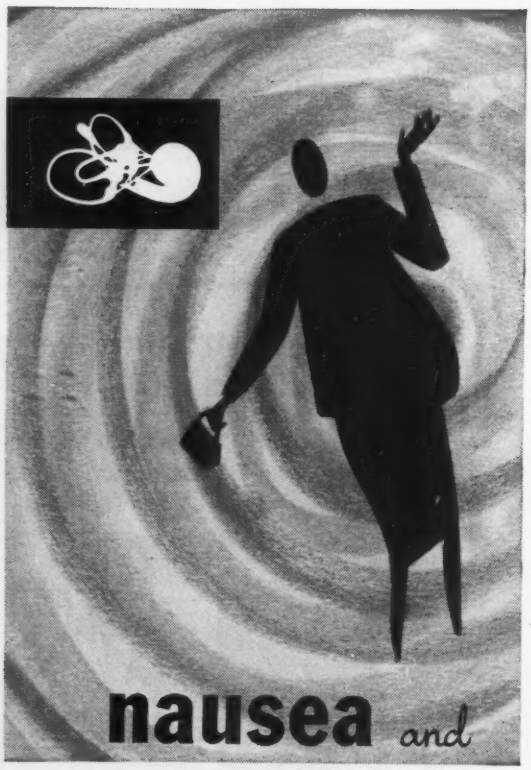

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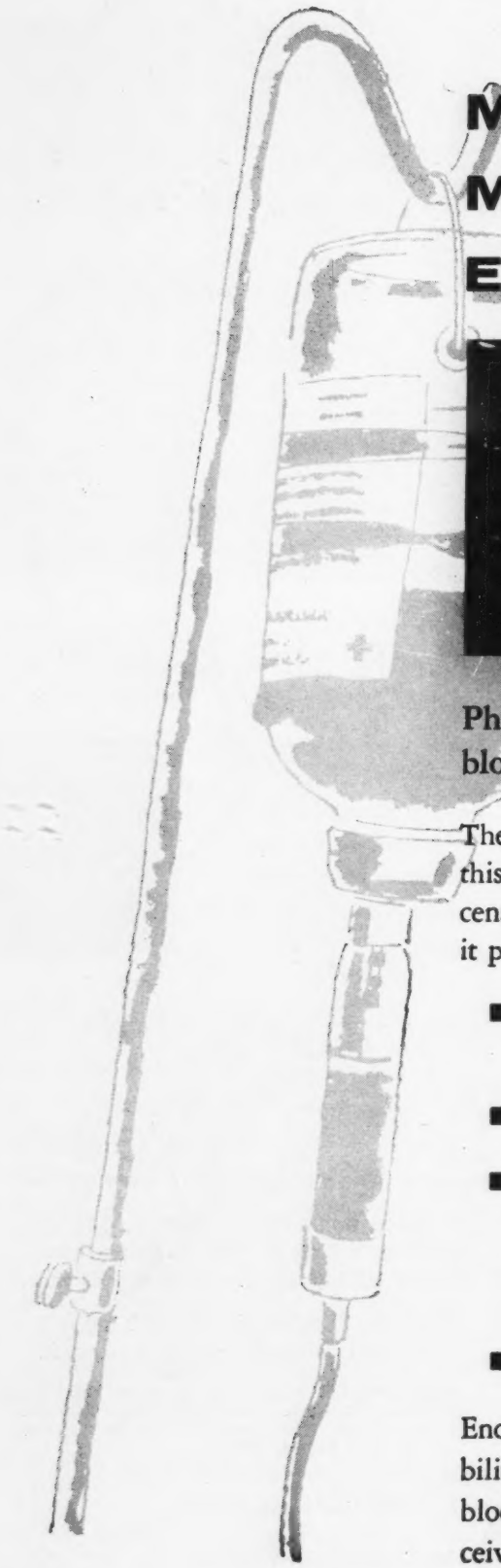

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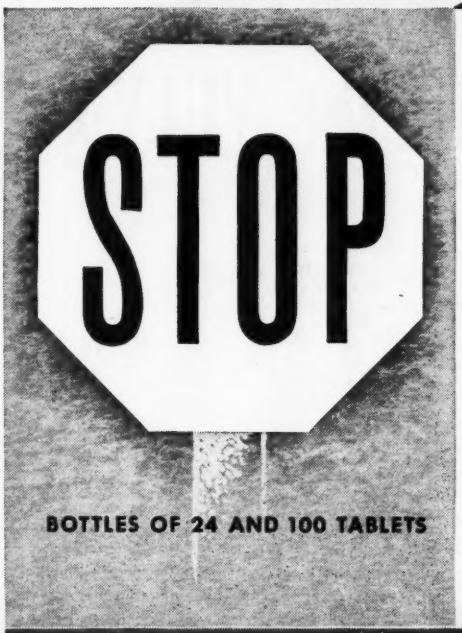

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